SUPPORTING INFORMATION

Novel machaeriol analogs as modulators of cannabinoid receptors – SAR of (+)-hexahydrocannabinoids and their isoform selectivities

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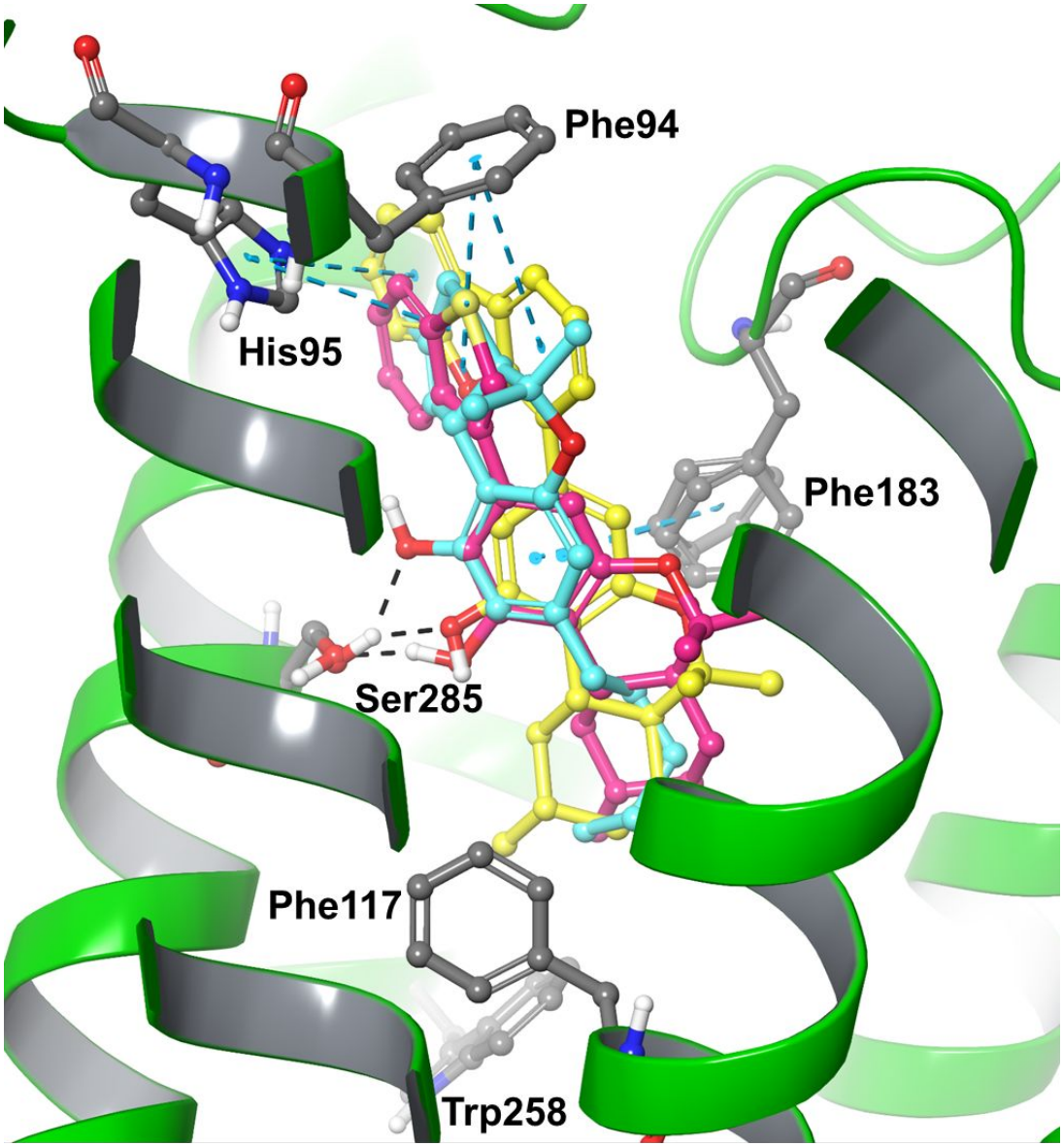


Figure S1. 3D overlaid representation of **11H** (carbon in yellow), **11J** (carbon in plum) and Δ^9-THC (carbon in cyan) against the CB_2 receptor. The key residues are shown in ball and stick model (carbon in grey).

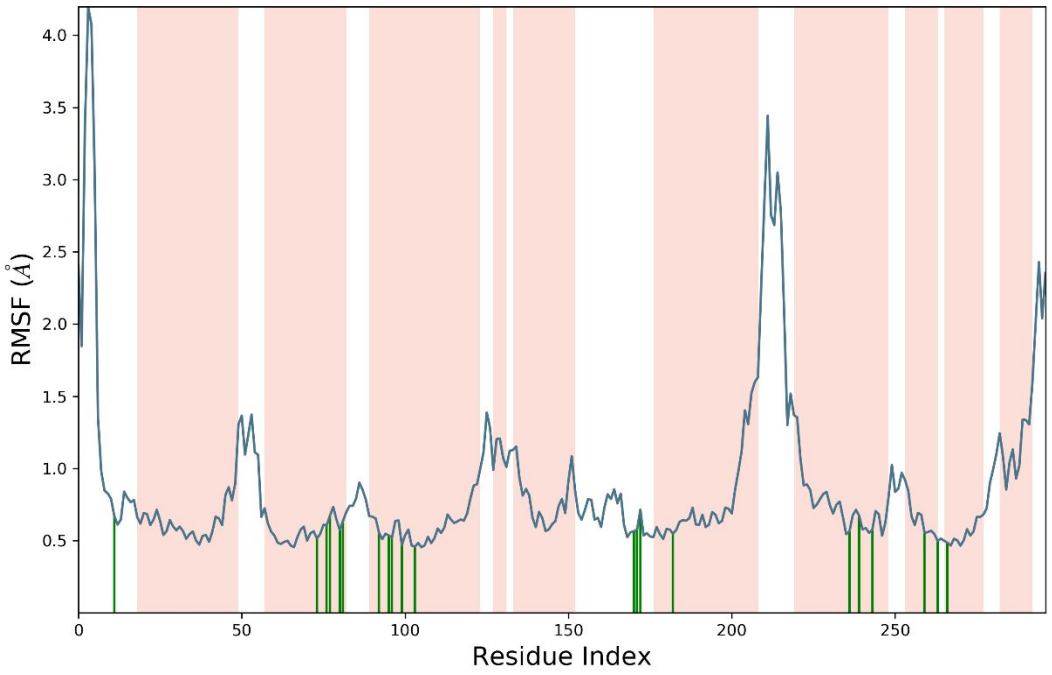


Figure S2. The Root Mean Square Fluctuation (RMSF) plot based on Cα atoms of the CB_1 receptor. Protein residues that interact with the **11J** is marked with green vertical bars.

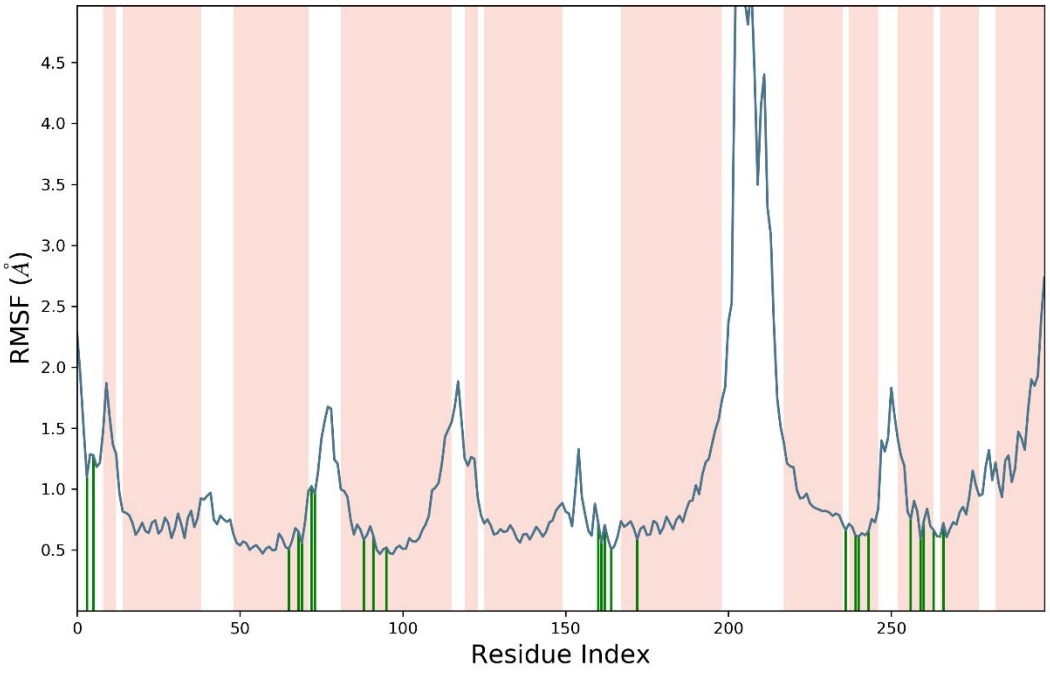


Figure S3. The Root Mean Square Fluctuation (RMSF) plot based on Cα atoms of the CB_2 receptor. Protein residues that interact with the **11J** are marked with green vertical bars.

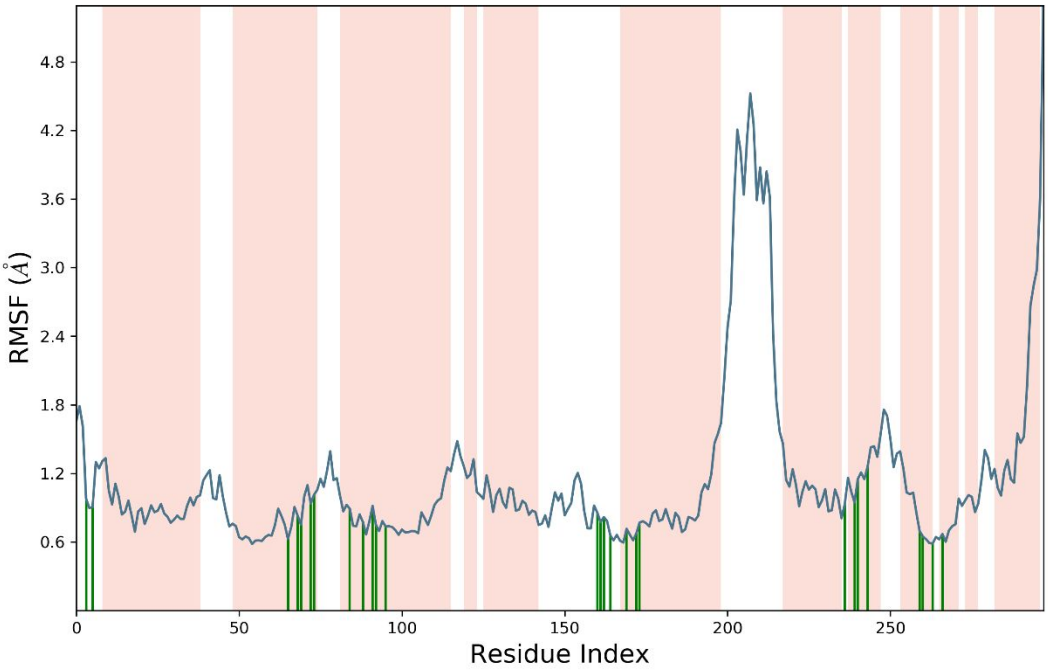


Figure S4. The Root Mean Square Fluctuation (RMSF) plot based on Cα atoms of the CB_2 receptor. Protein residues that interact with the **11H** is marked with green vertical bars.

Figure S5a. ^{1}H NMR spectra of compound **11A**

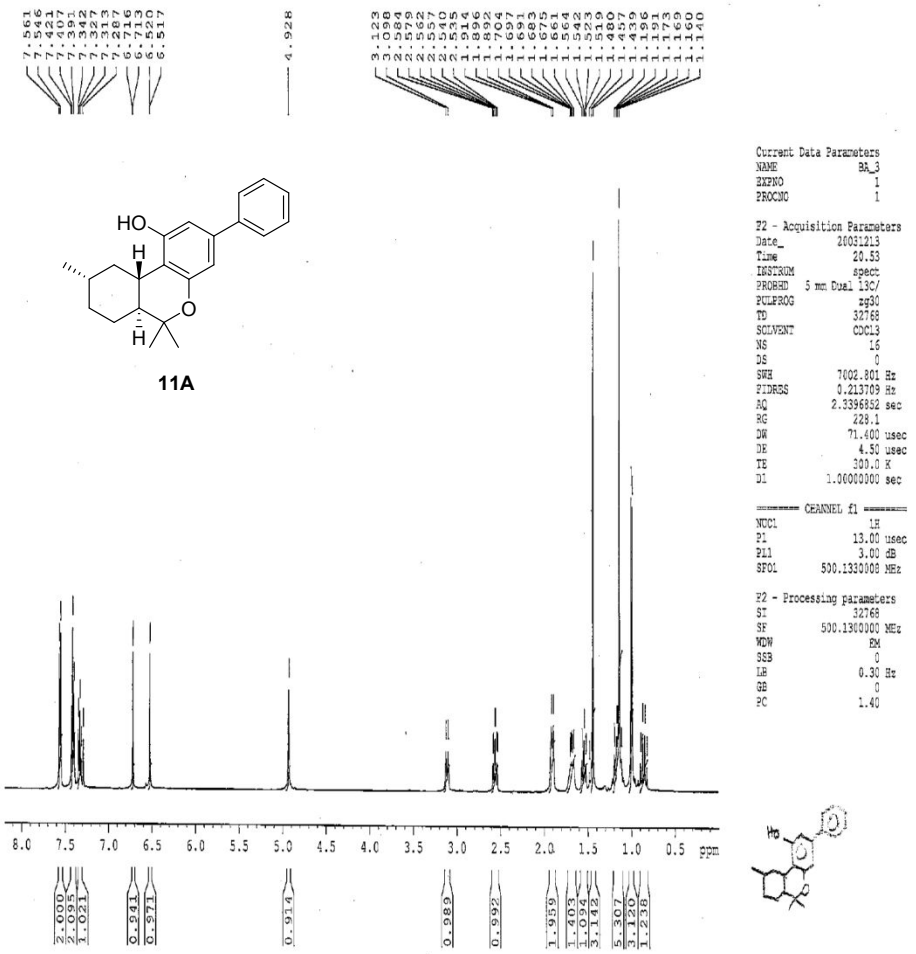


Figure S5b. ^{13}C NMR spectra of compound **11A**

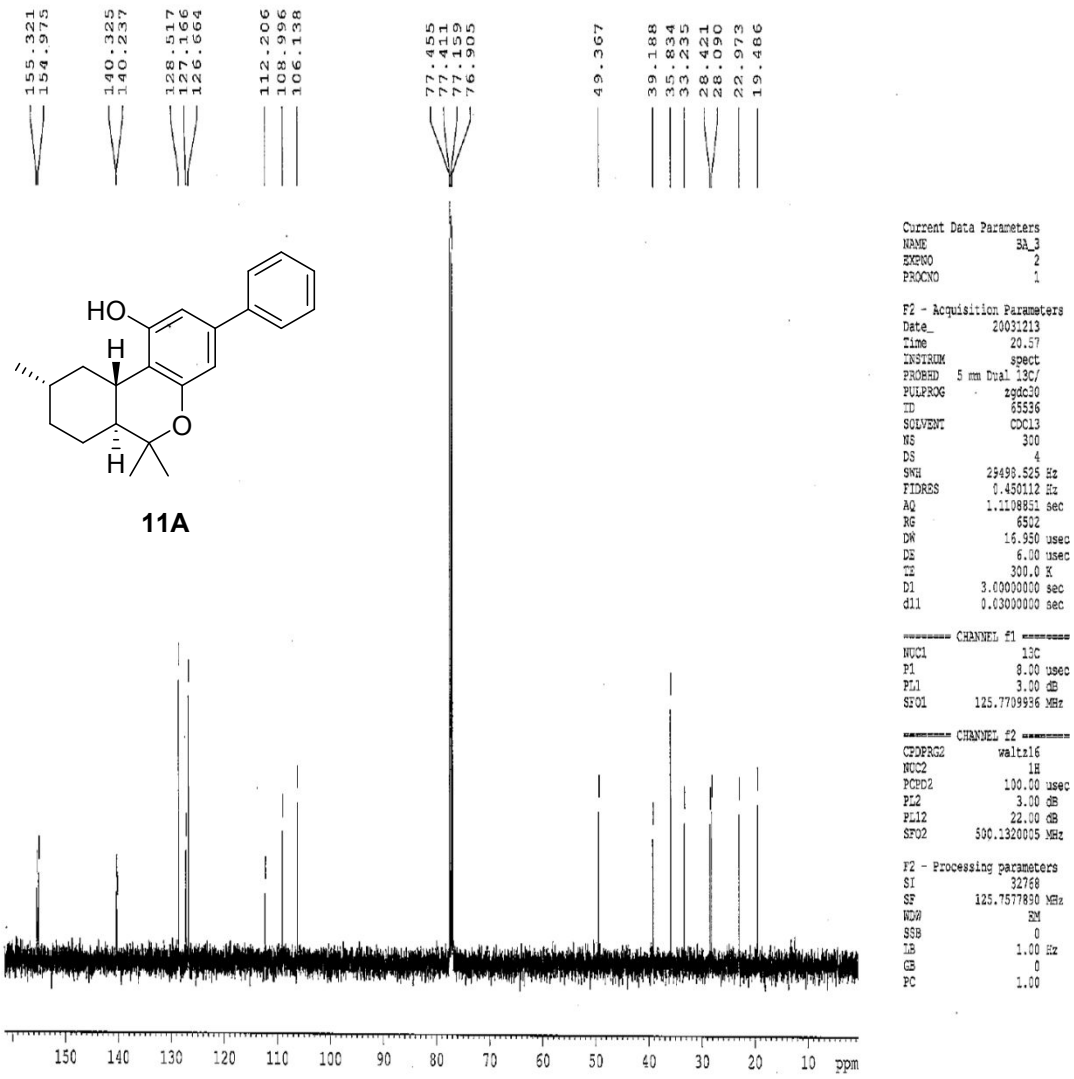


Figure S5c. DEPT-135 NMR spectra of compound **11A**

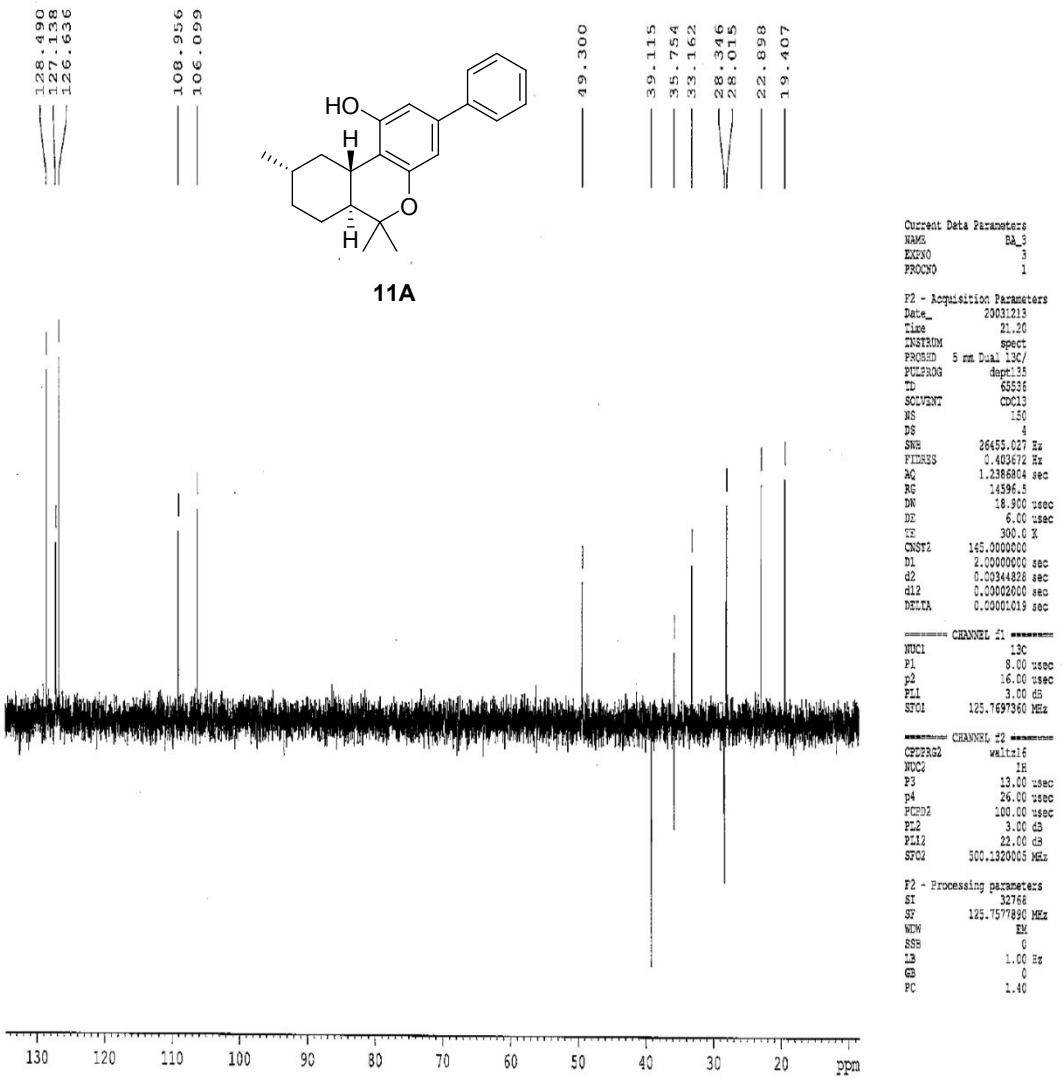
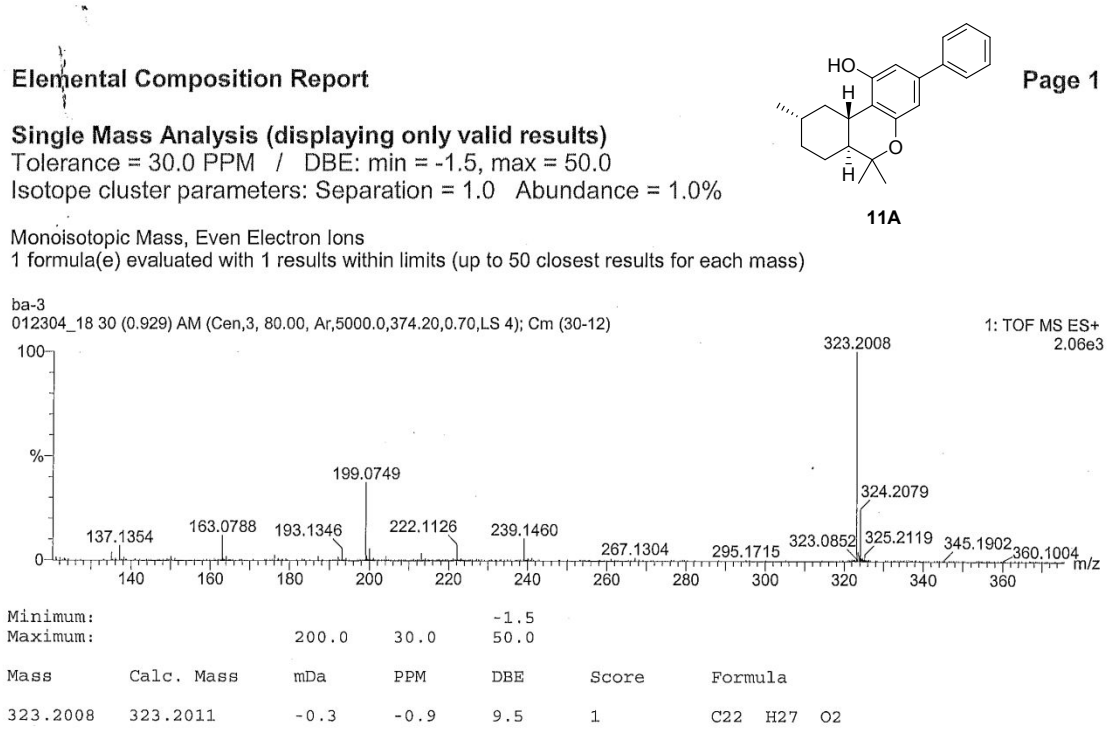


Figure S5d. HR-MS of compound **11A**



Minimum:				-1.5		
Maximum:		200.0	30.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
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Figure S6a. [1]H NMR spectra of compound **11B**

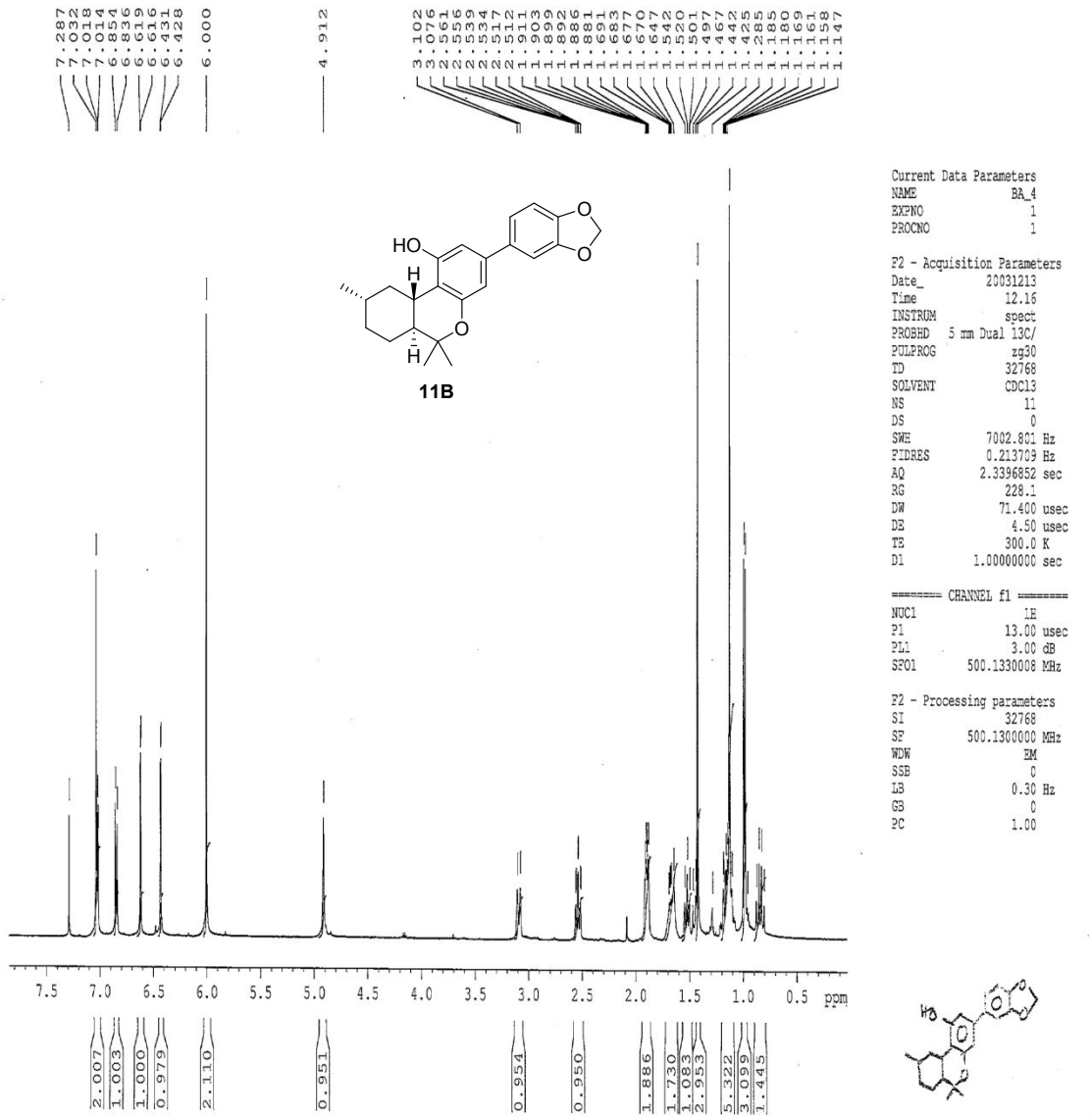

Figure S6b. ^{13}C NMR spectra of compound **11B**

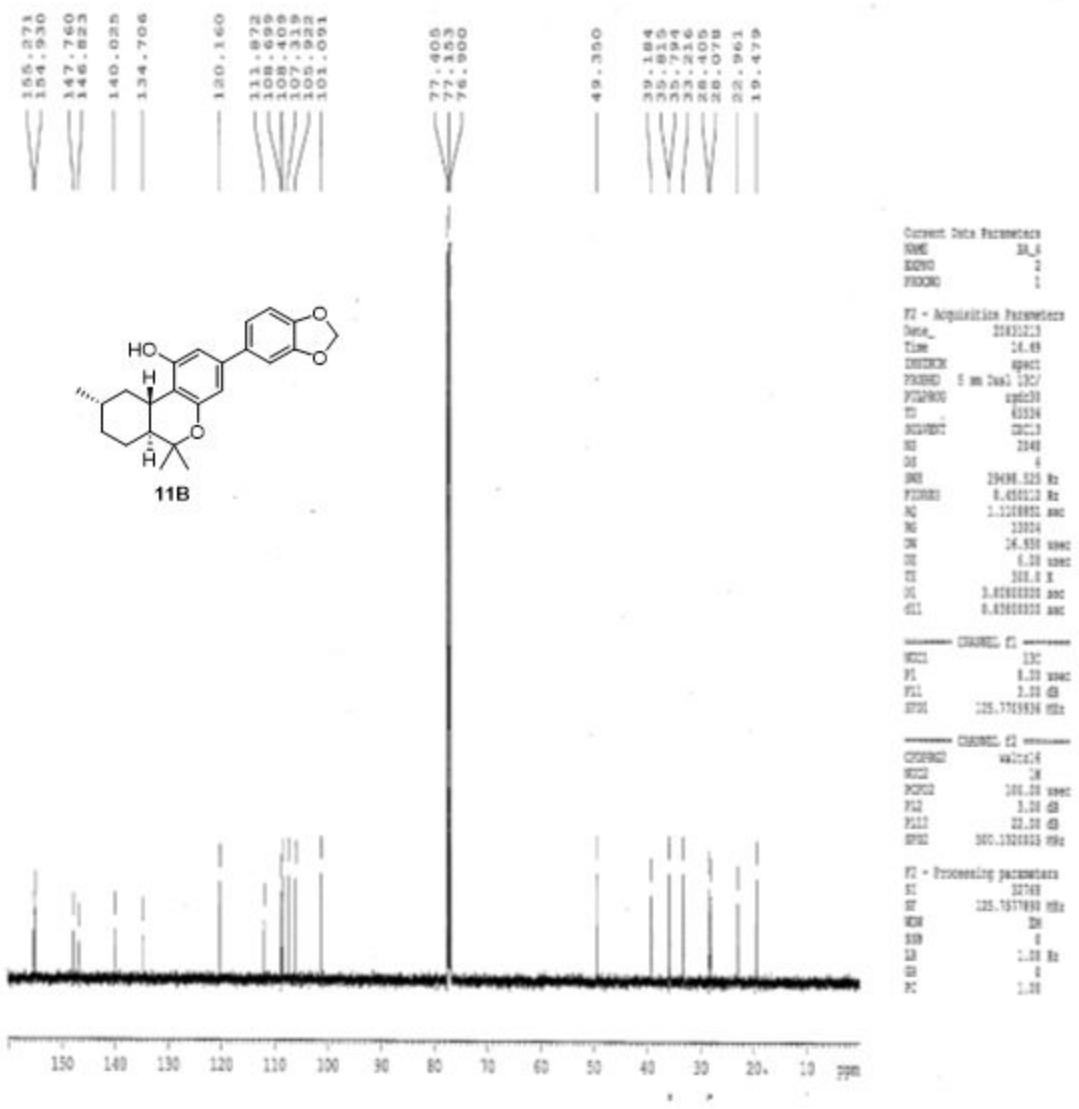

Figure S6c. DEPT-135 NMR spectra of compound **11B**

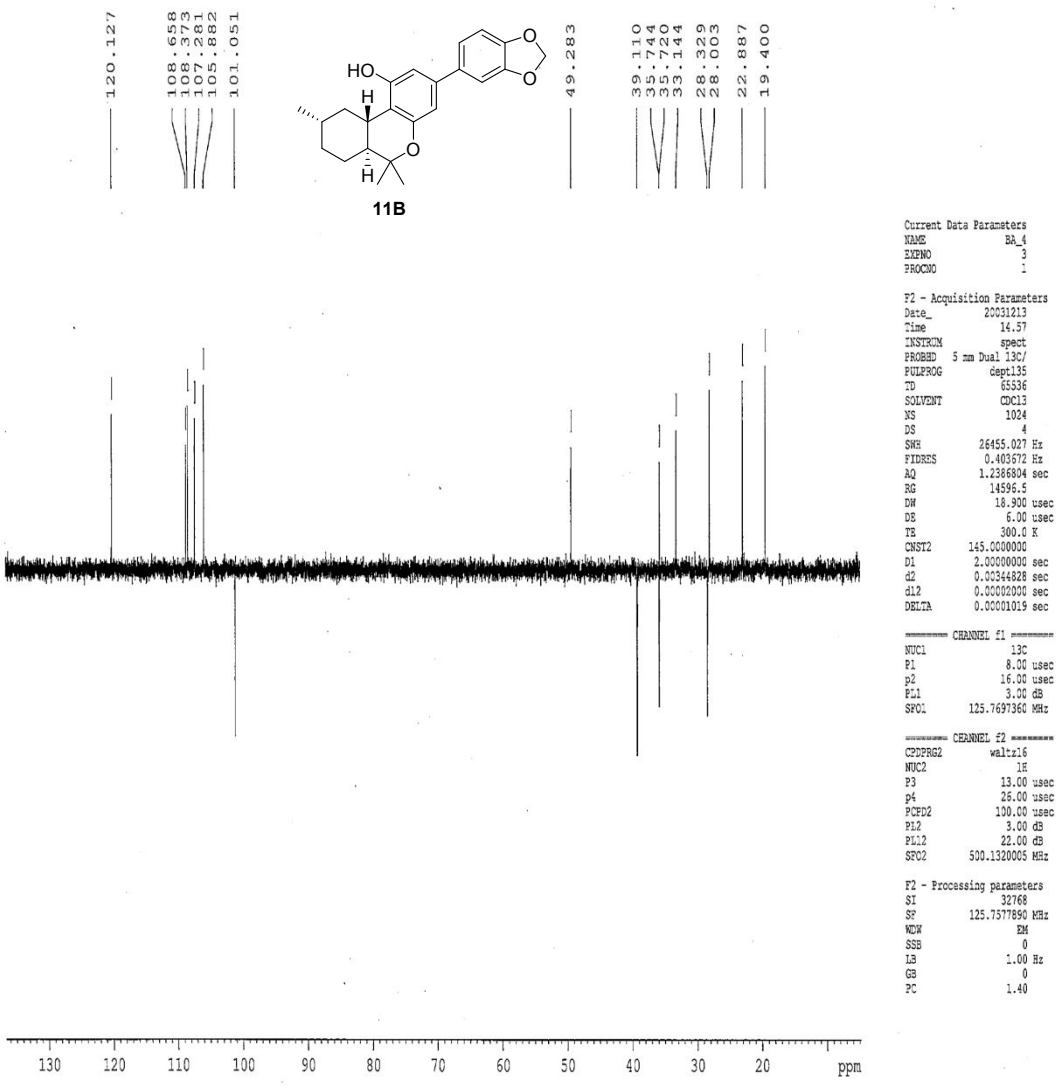

Figure S6d. HR-MS of compound **11B**

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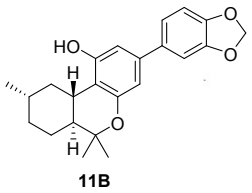
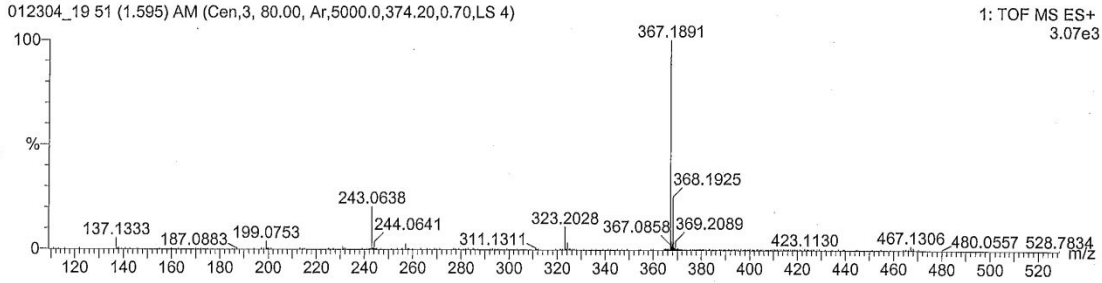


11B

Single Mass Analysis (displaying only valid results)
Tolerance = 30.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

ba-4
012304_19 51 (1.595) AM (Cen,3, 80.00, Ar,5000.0,374.20,0.70,LS 4)



Minimum:				-1.5		
Maximum:		200.0	30.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula

Figure S7a. [1]H NMR spectra of compound **11C**

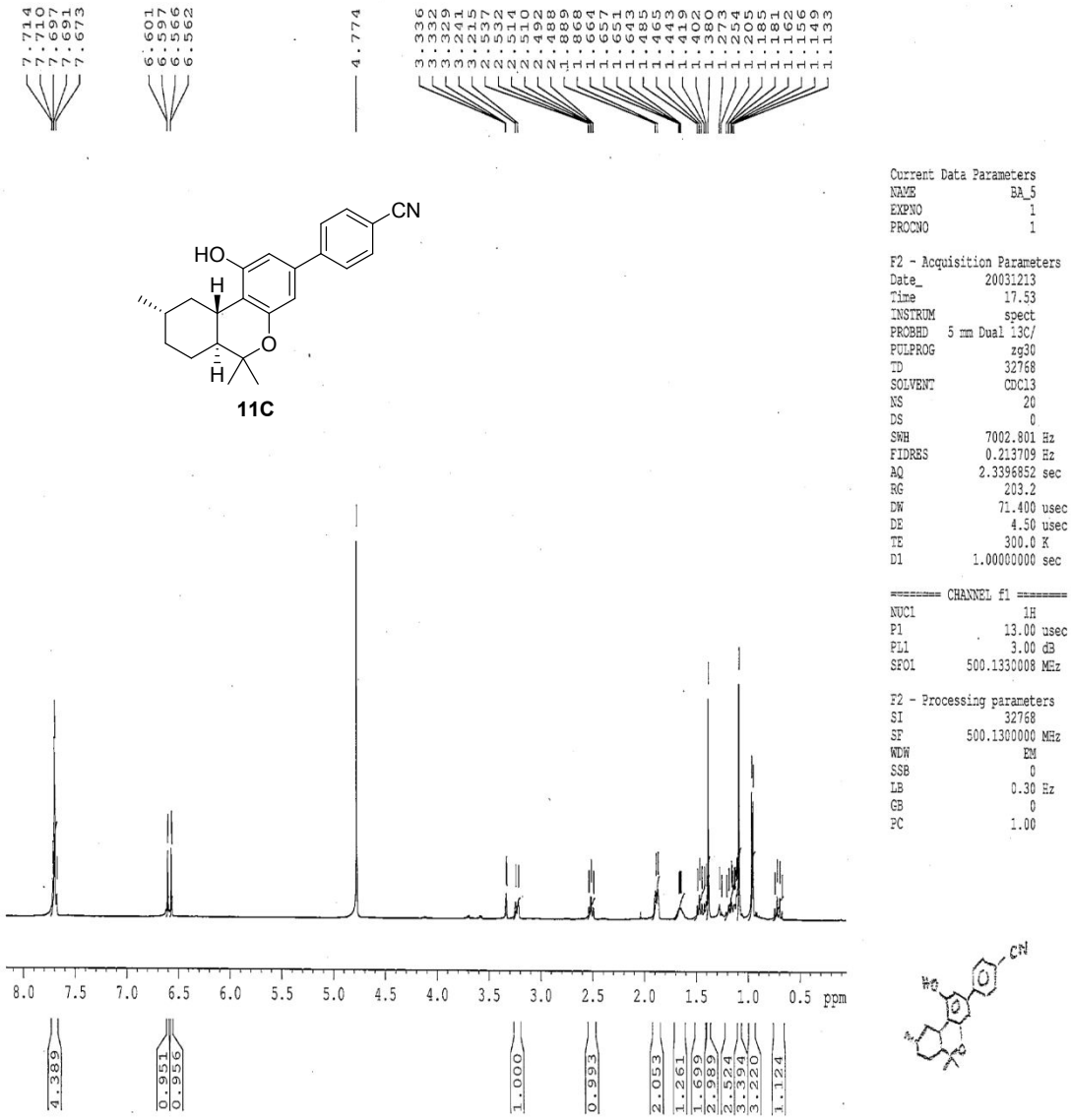


Figure S7b. ^{13}C NMR spectra of compound **11C**

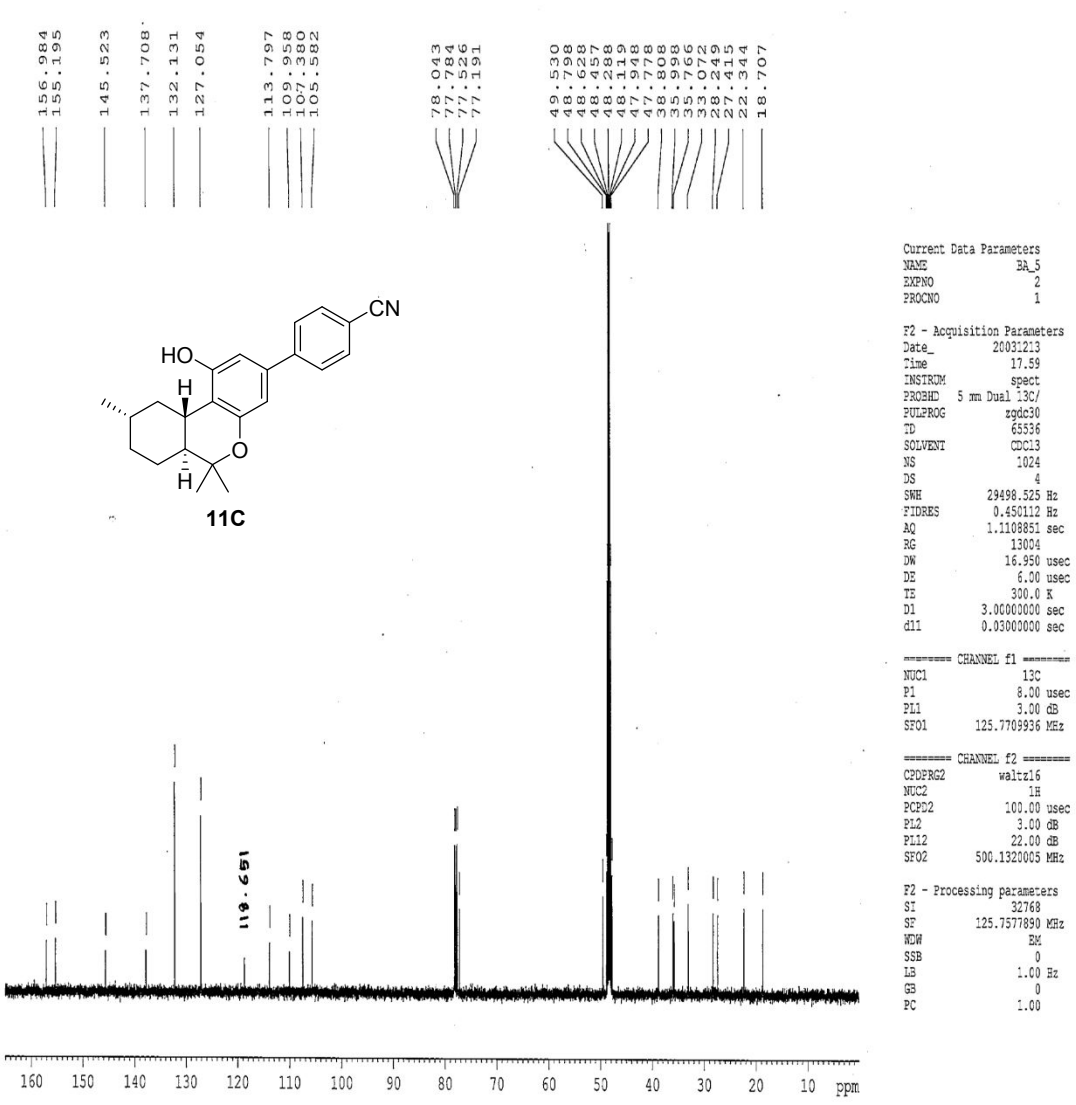


Figure S7c. DEPT-135 NMR spectra of compound **11C**

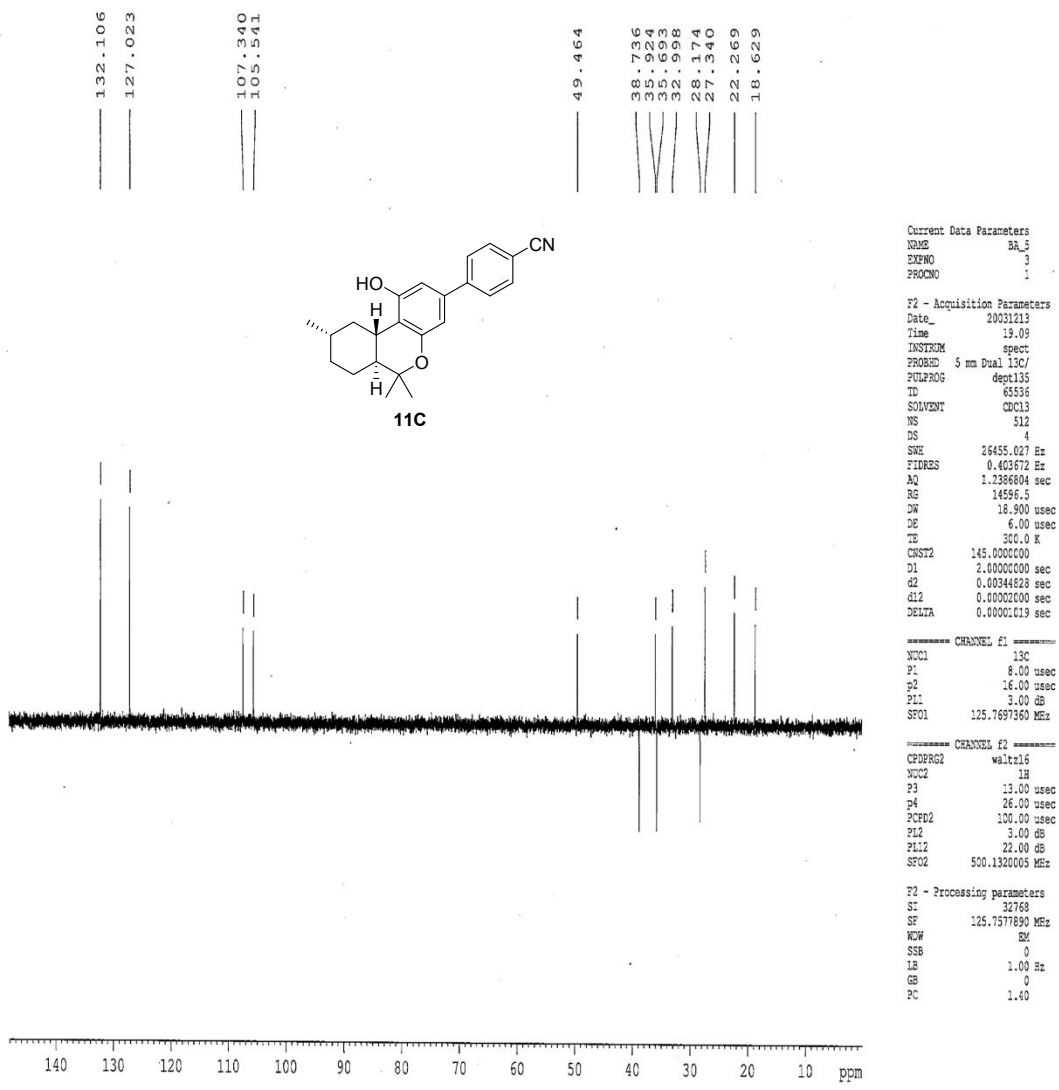
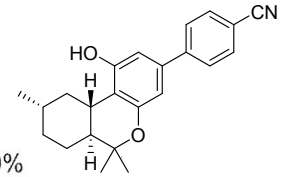


Figure S7d. HR-MS of compound **11C**



11C

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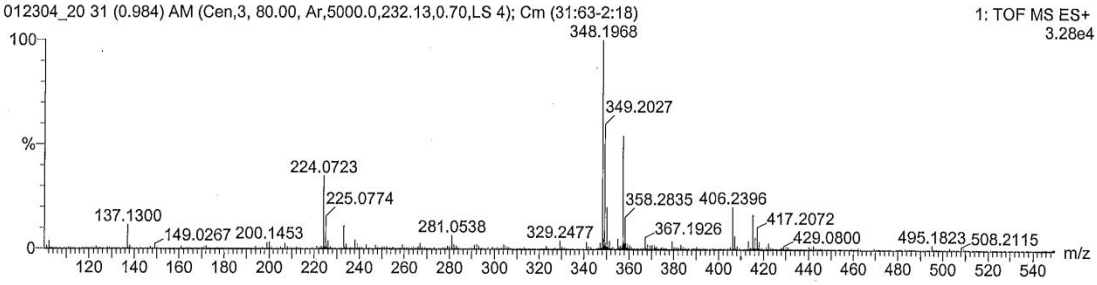
Single Mass Analysis (displaying only valid results)
Tolerance = 30.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Even Electron Ions
3 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

ba-5
012304_20 31 (0.984) AM (Cen,3, 80.00, Ar,5000.0,232.13,0.70,LS 4); Cm (31:63-2:18)

1: TOF MS ES+
3.28e4



Minimum:				-1.5		
Maximum:		200.0	30.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
348.1968	348.1964	0.5	1.3	11.5	1	C23 H26 N O2

Figure S8a. [1]H NMR spectra of compound **11D**

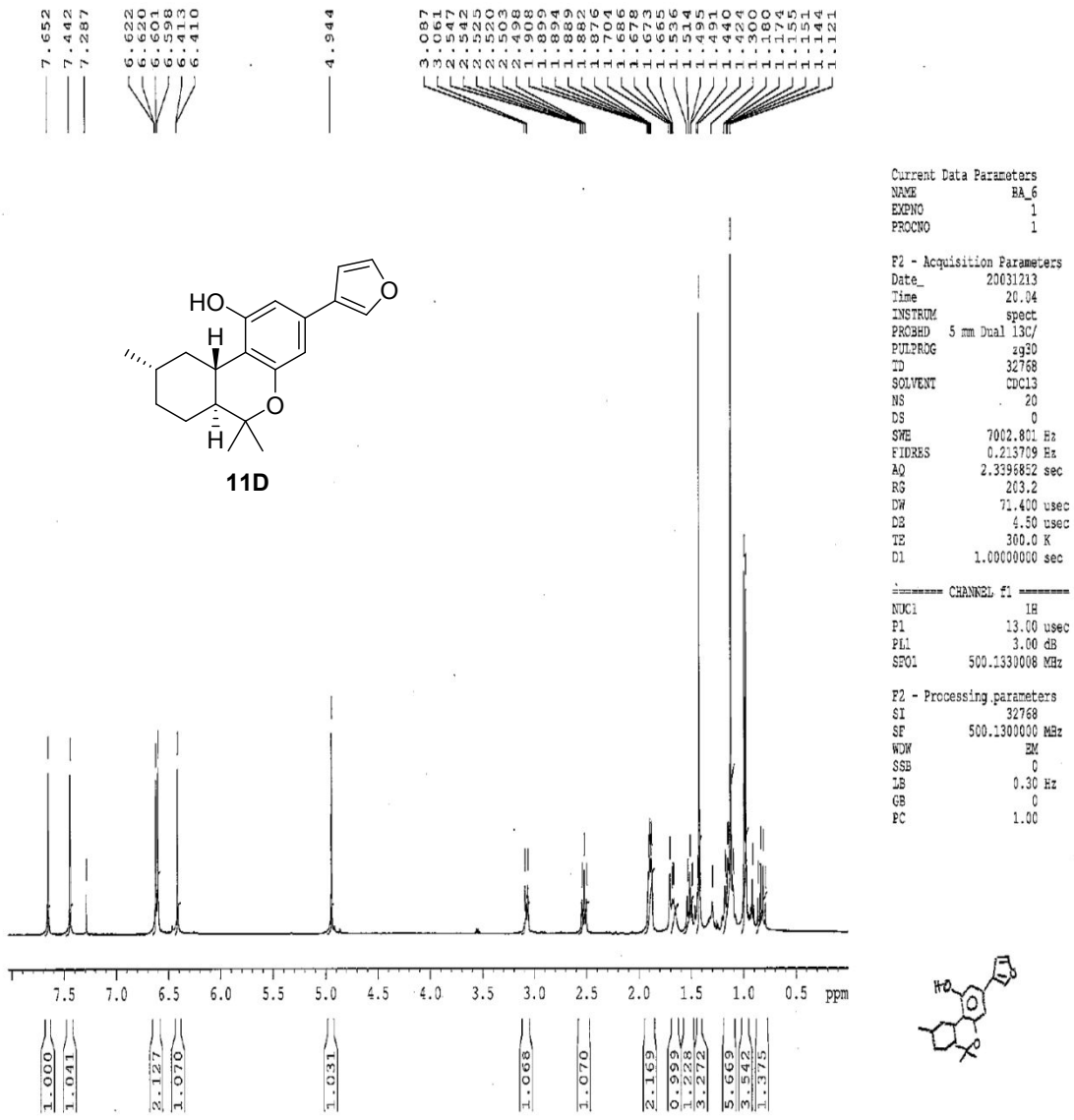


Figure S8b. ^{13}C NMR spectra of compound **11D**

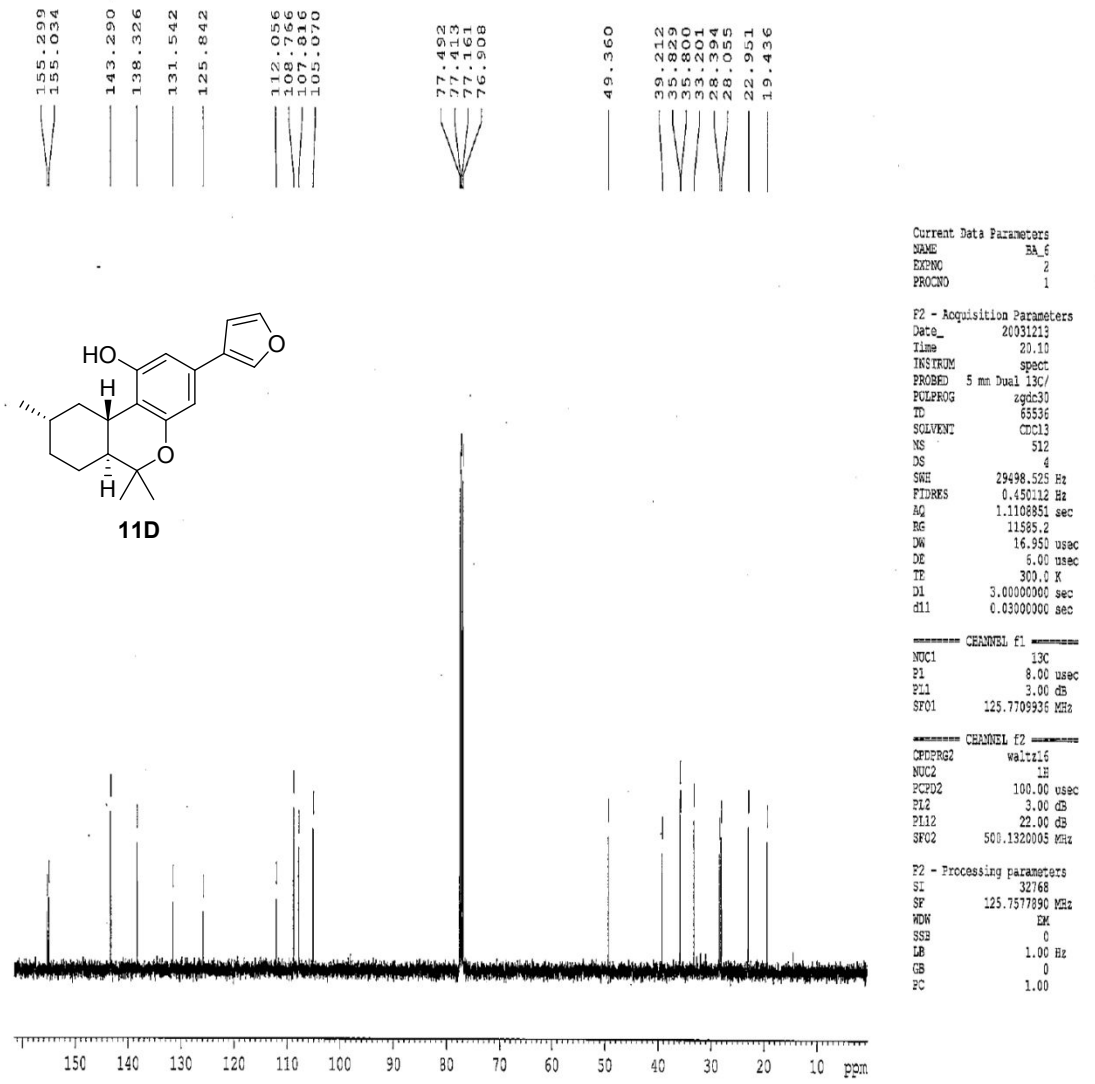


Figure S8c. DEPT-135 NMR spectra of compound **11D**

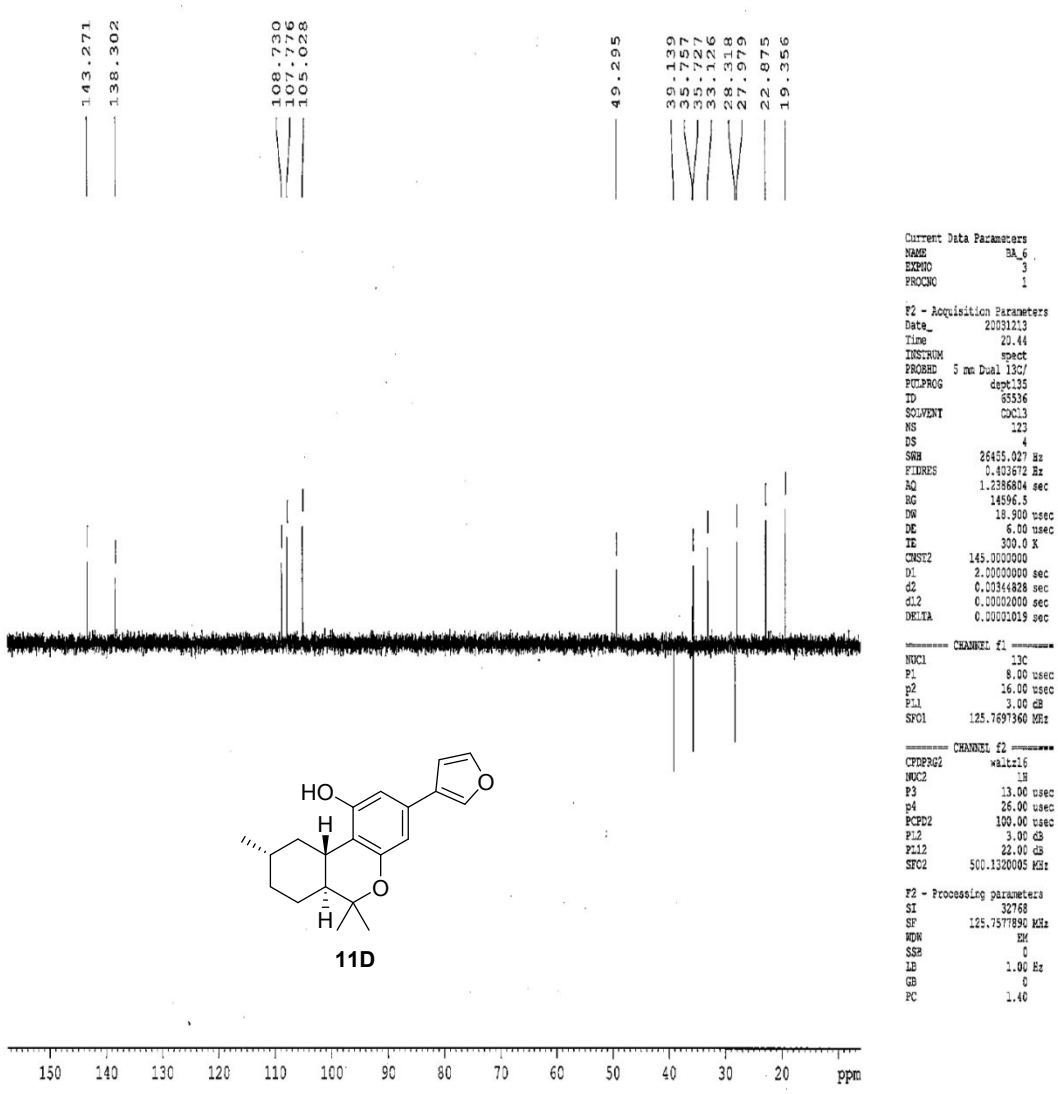


Figure S8d. HR-MS of compound **11D**

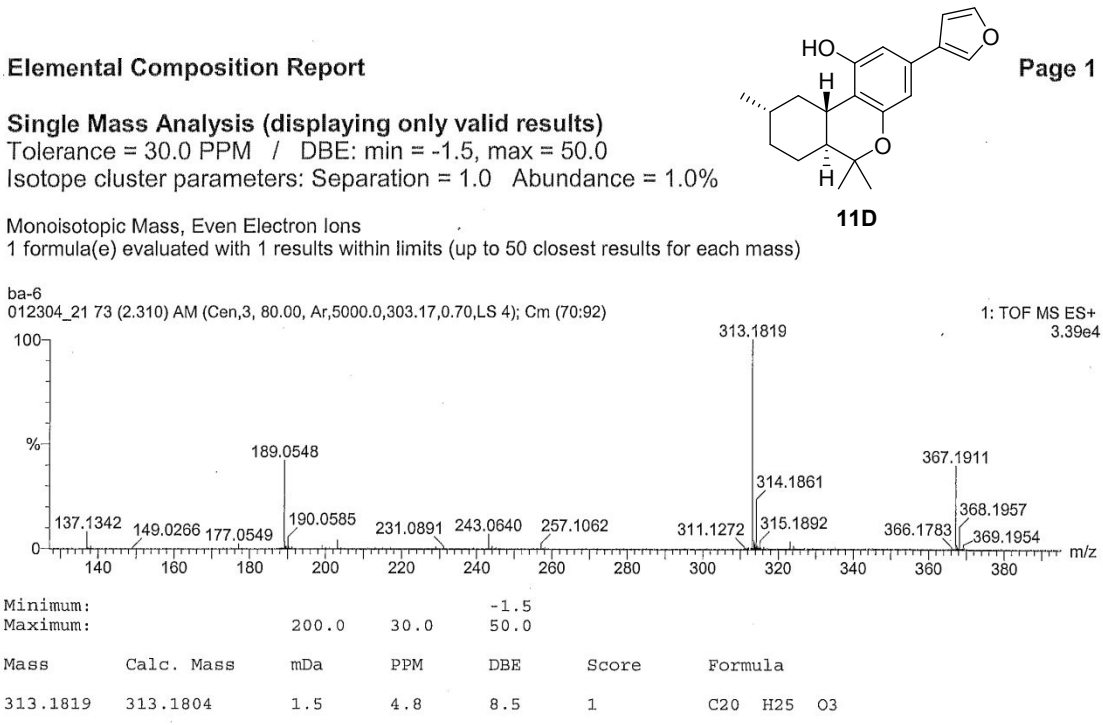


Figure S9a. [1]H NMR spectra of compound **11E**

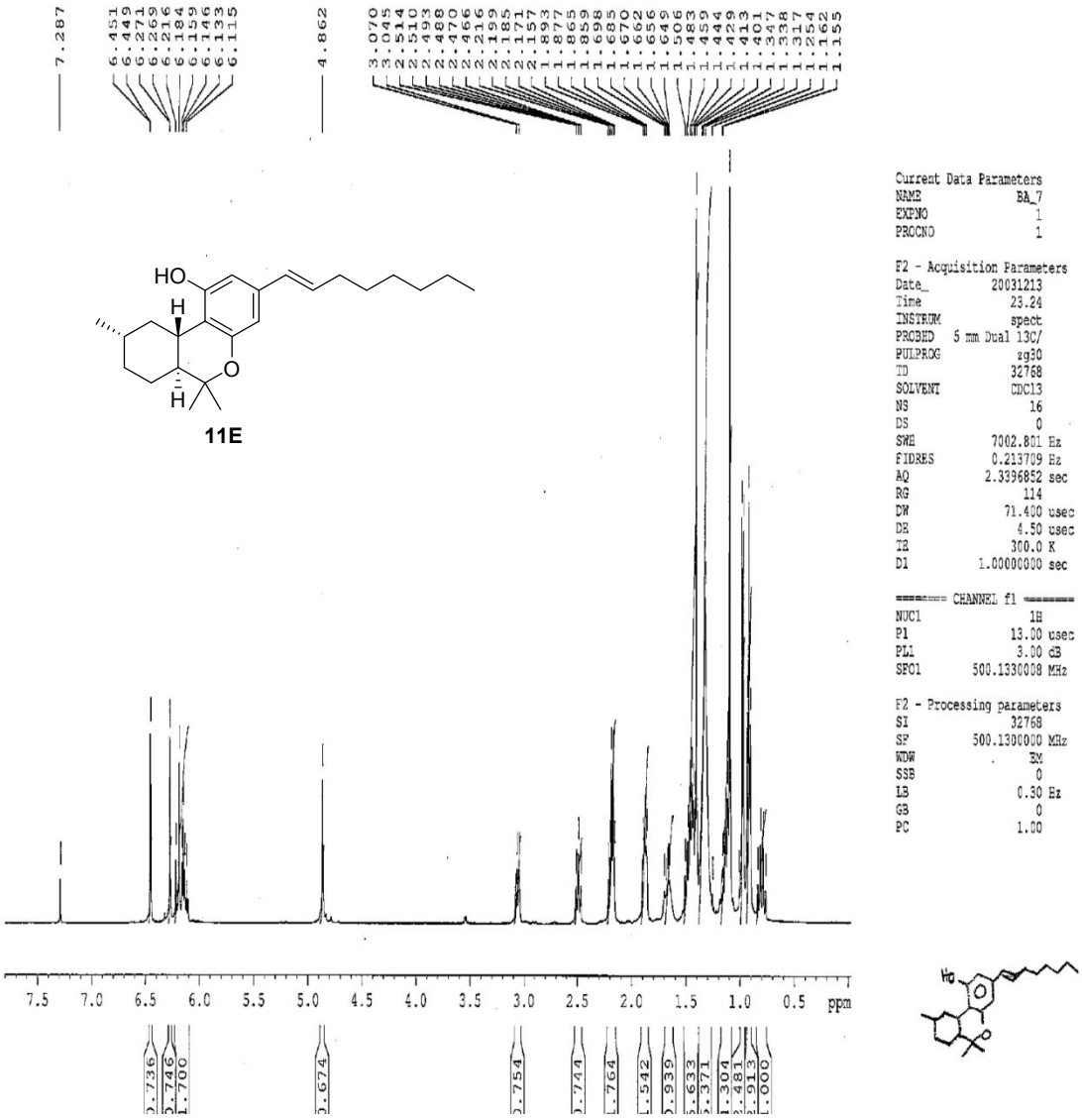


Figure S9b. ^{13}C NMR spectra of compound **11E**

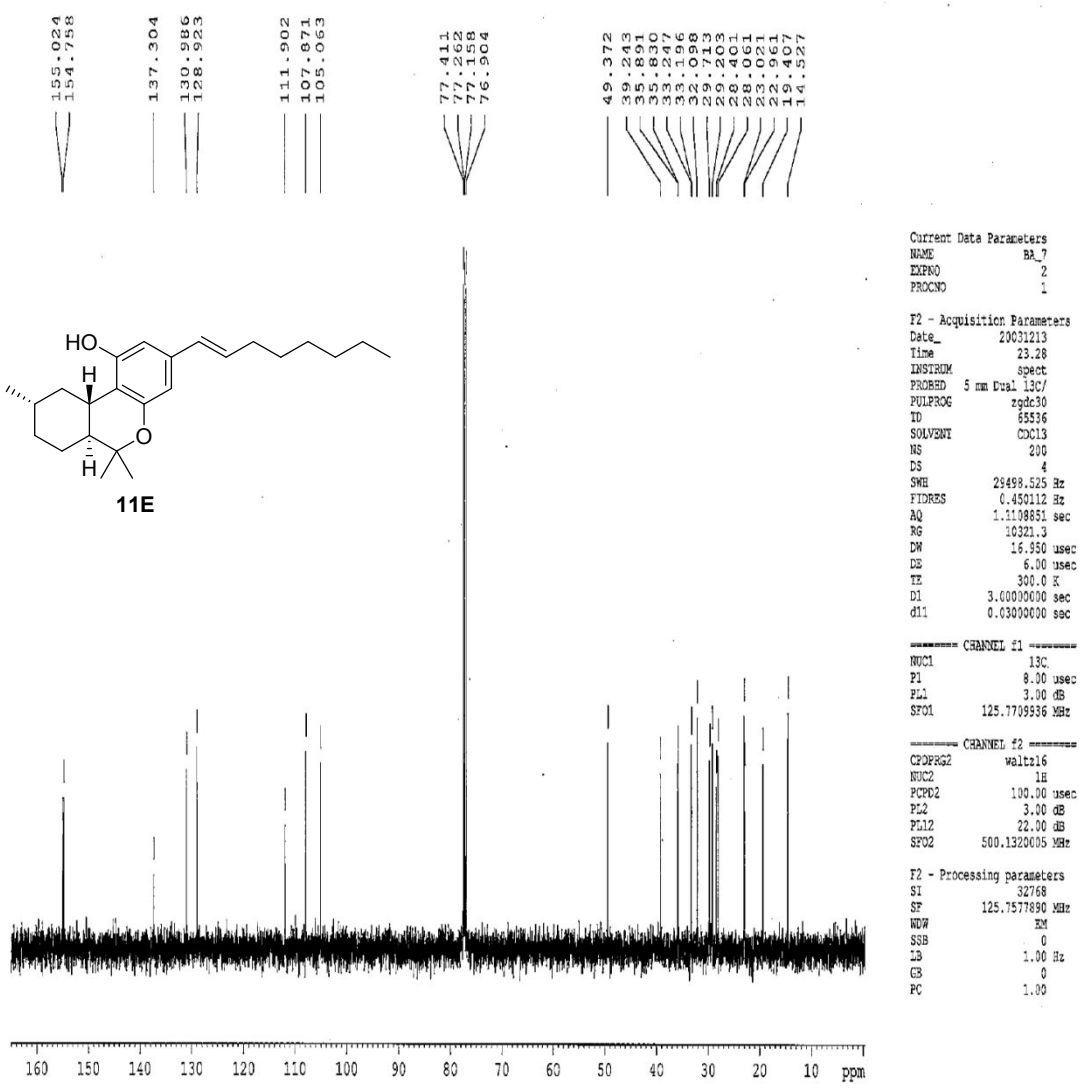


Figure S9c. DEPT-135 NMR spectra of compound **11E**

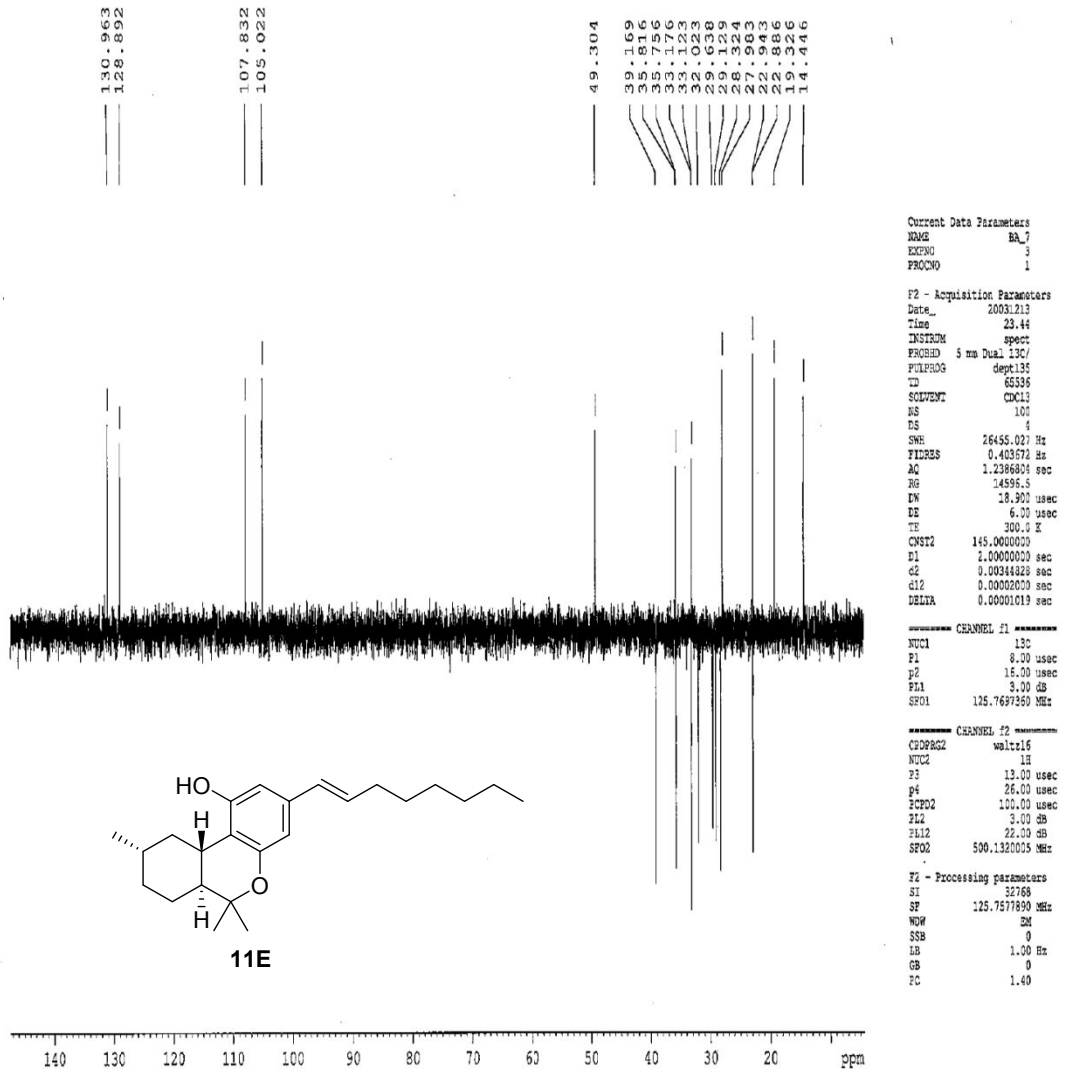


Figure S9d. HR-MS of compound **11E**

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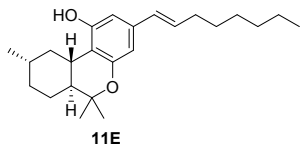
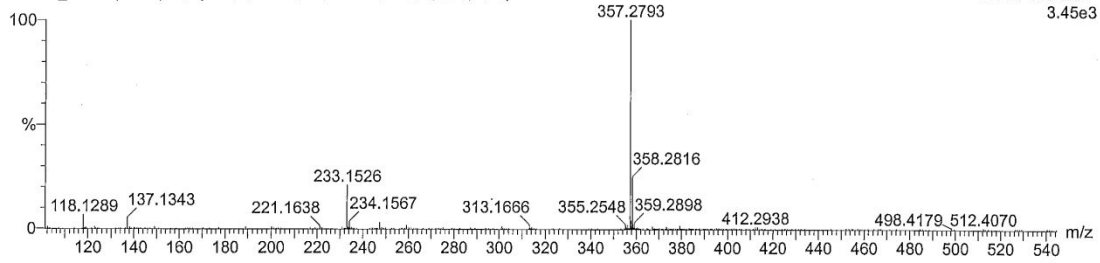


11E

Single Mass Analysis (displaying only valid results)
Tolerance = 30.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

ba-7
012304_22 42 (1.309) AM (Cen,3, 80.00, Ar,5000.0,303.17,0.70,LS 4)



Minimum:				-1.5		
Maximum:		200.0	30.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
357.2793	357.2794	-0.1	-0.2	6.5	1	C24 H37 O2

Figure S10a. ^{1}H NMR spectra of compound **11F**

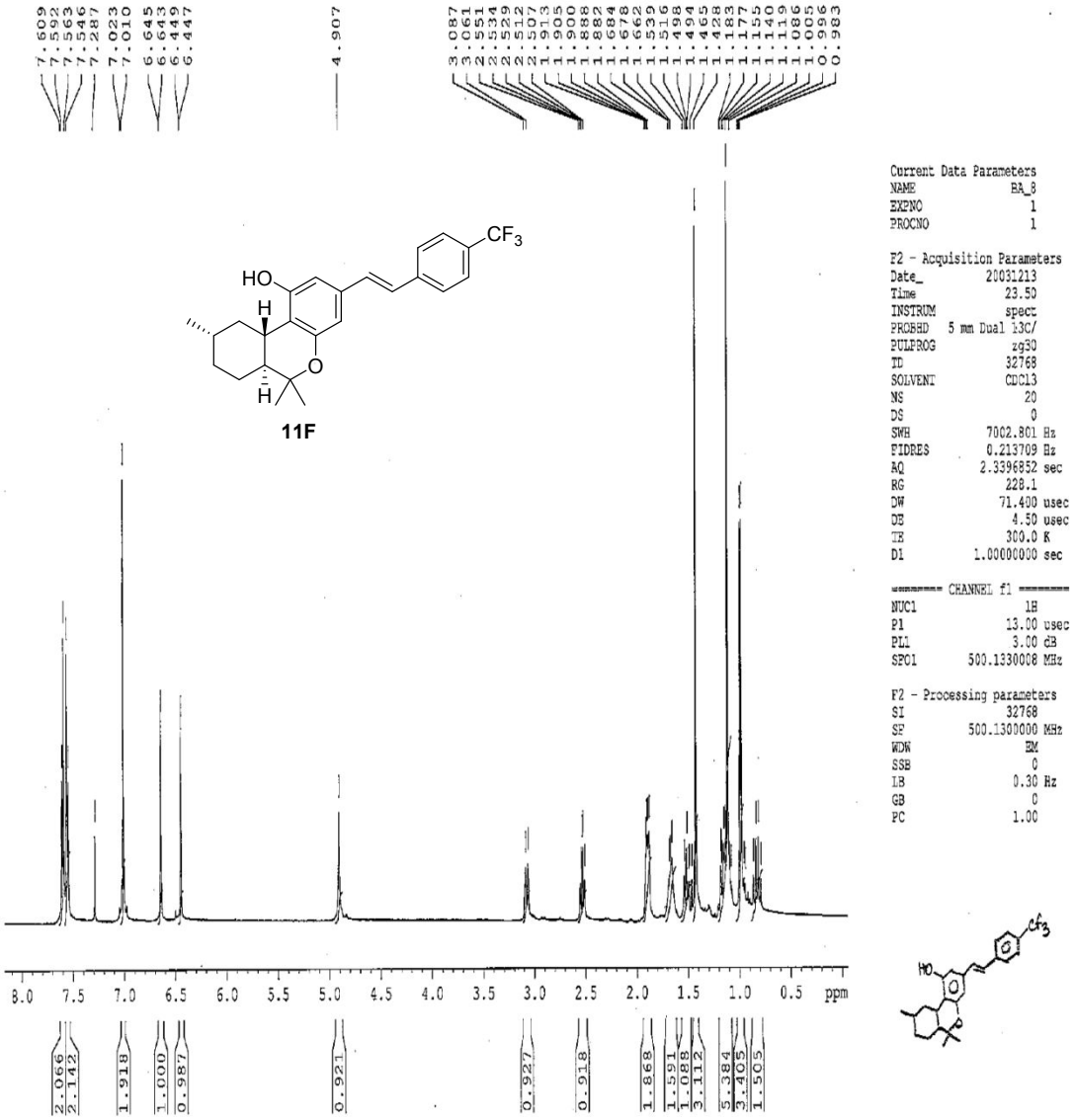


Figure S10b. ^{13}C NMR spectra of compound **11F**

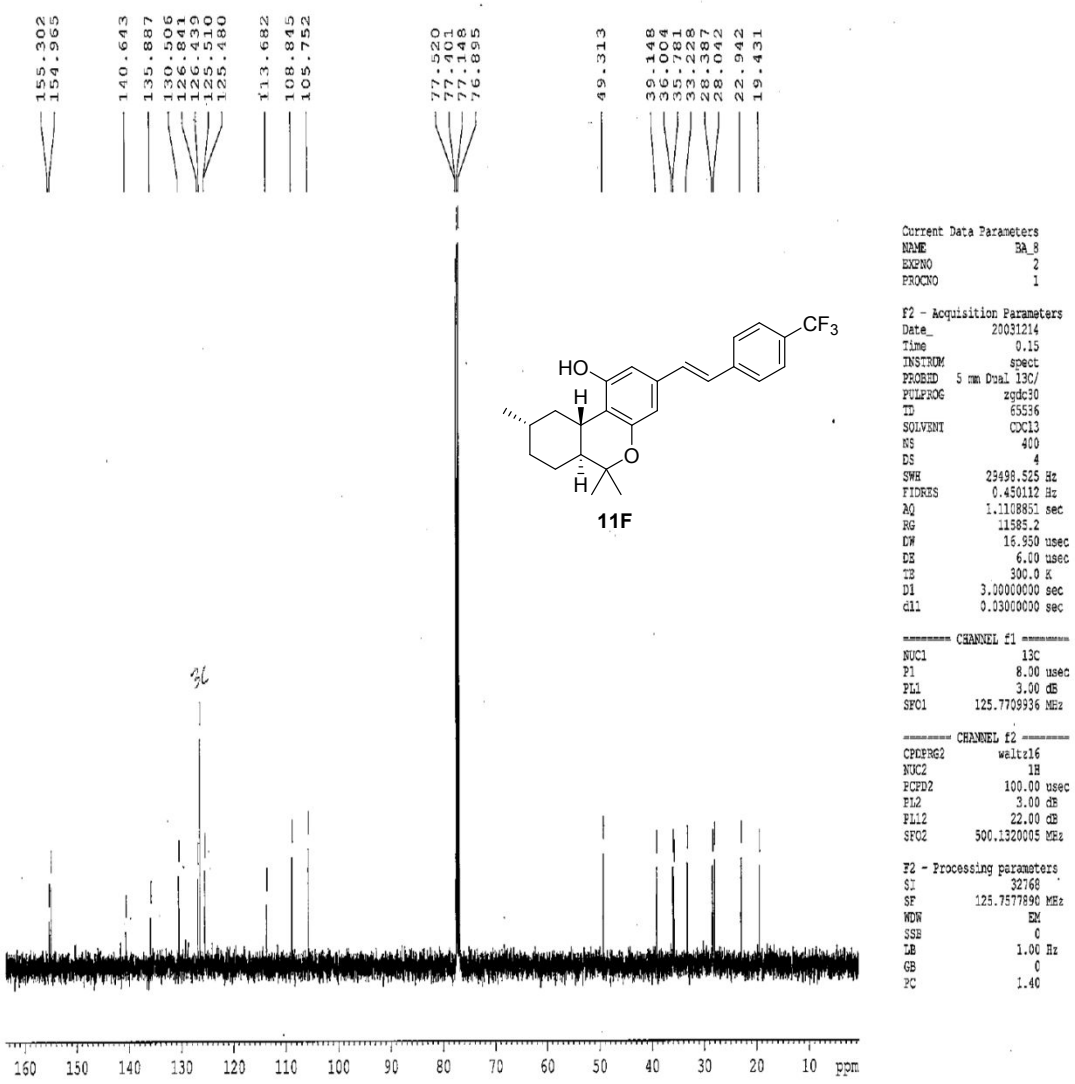


Figure S10c. DEPT-135 NMR spectra of compound **11F**

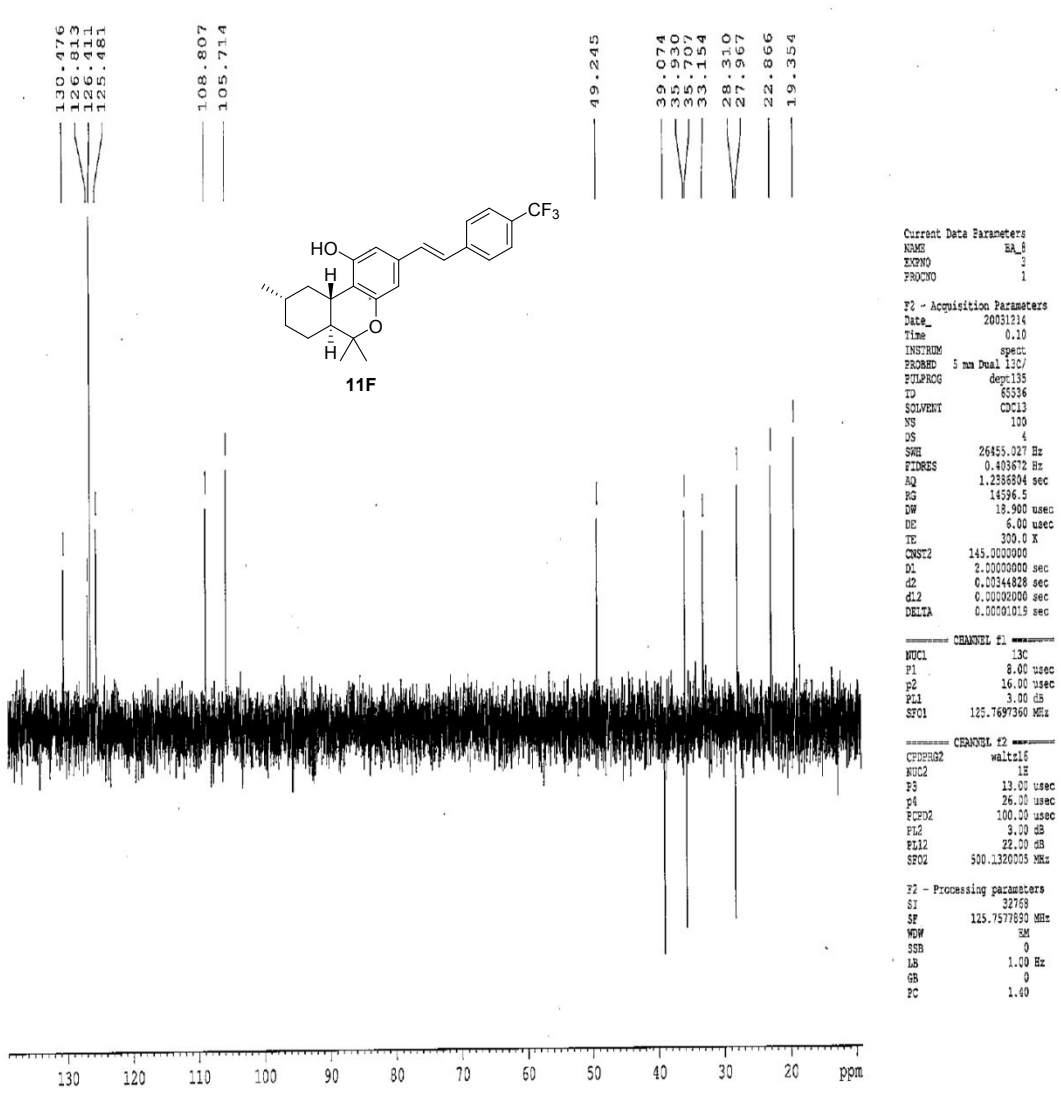
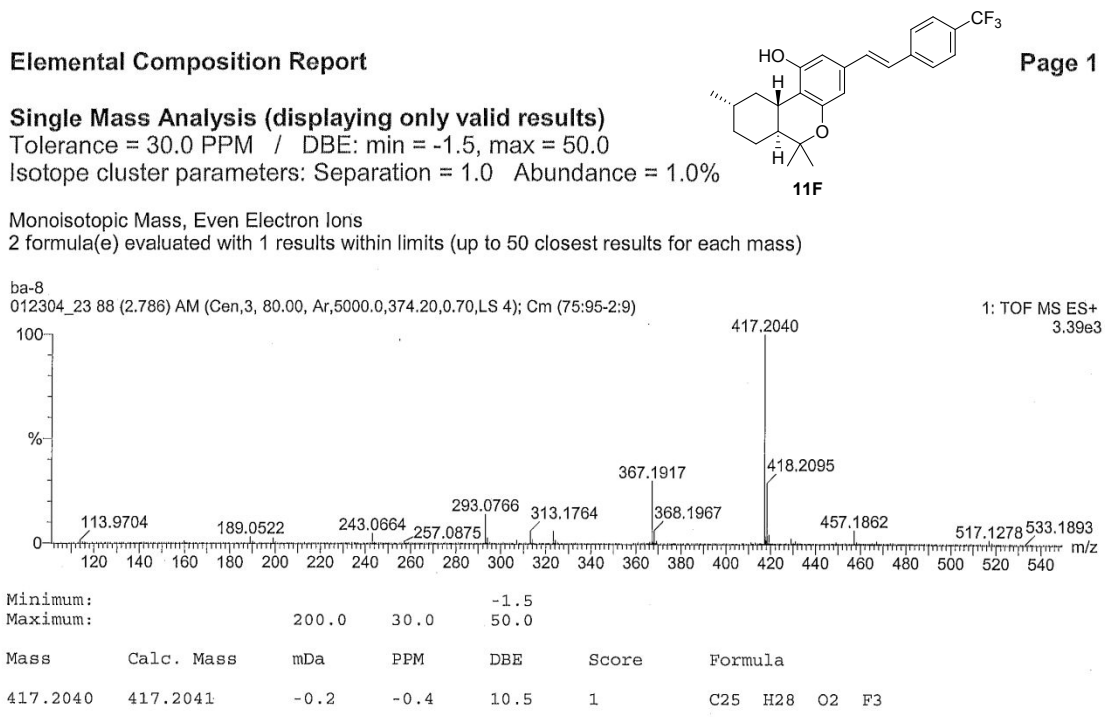


Figure S10d. HR-MS of compound **11F**



Minimum:				-1.5		
Maximum:		200.0	30.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
417.2040	417.2041	-0.2	-0.4	10.5	1	C25 H28 O2 F3

Figure S11a. [1]H NMR spectra of compound **11G**

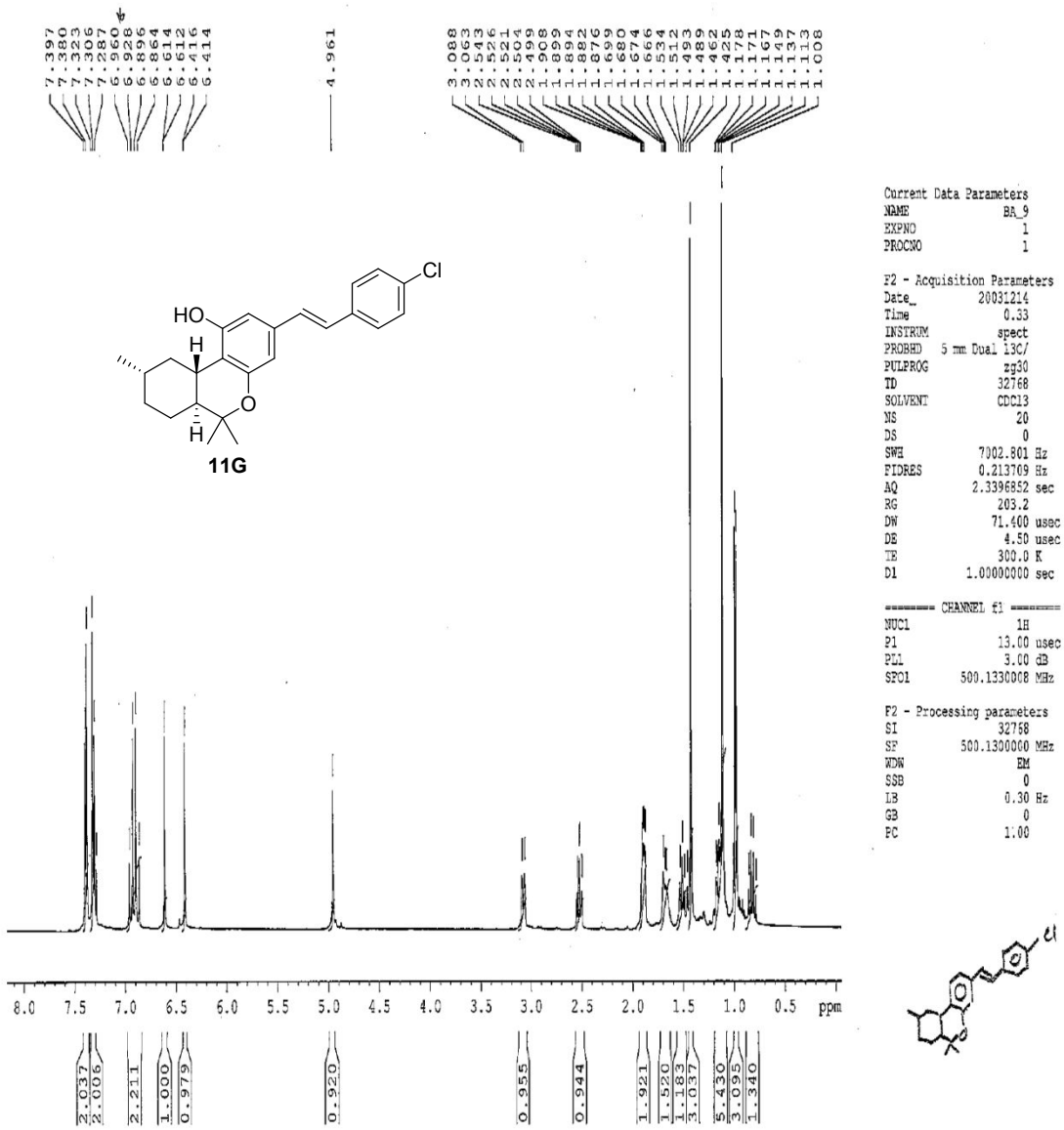


Figure S11b. ^{13}C NMR spectra of compound **11G**

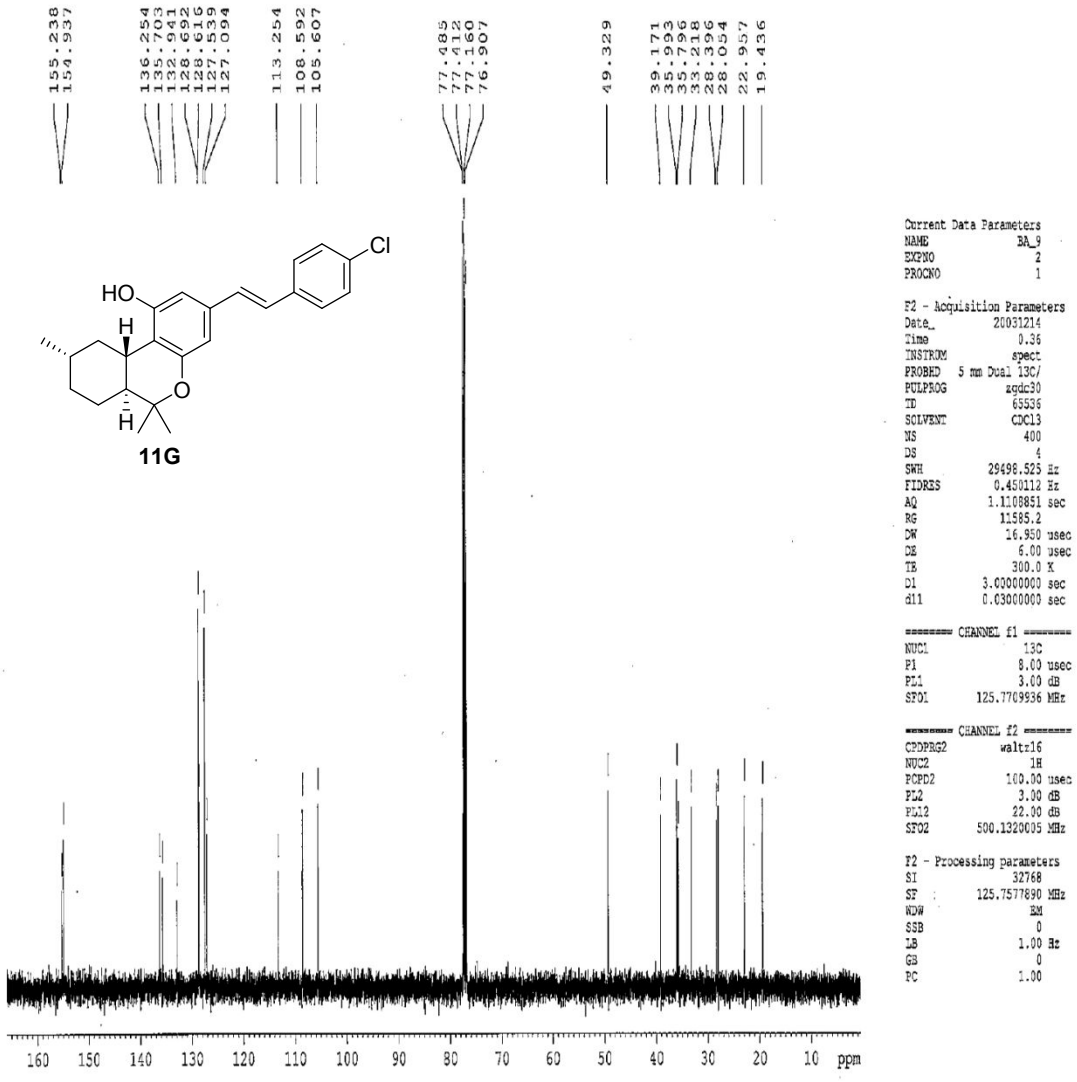


Figure S11c. DEPT-135 NMR spectra of compound **11G**

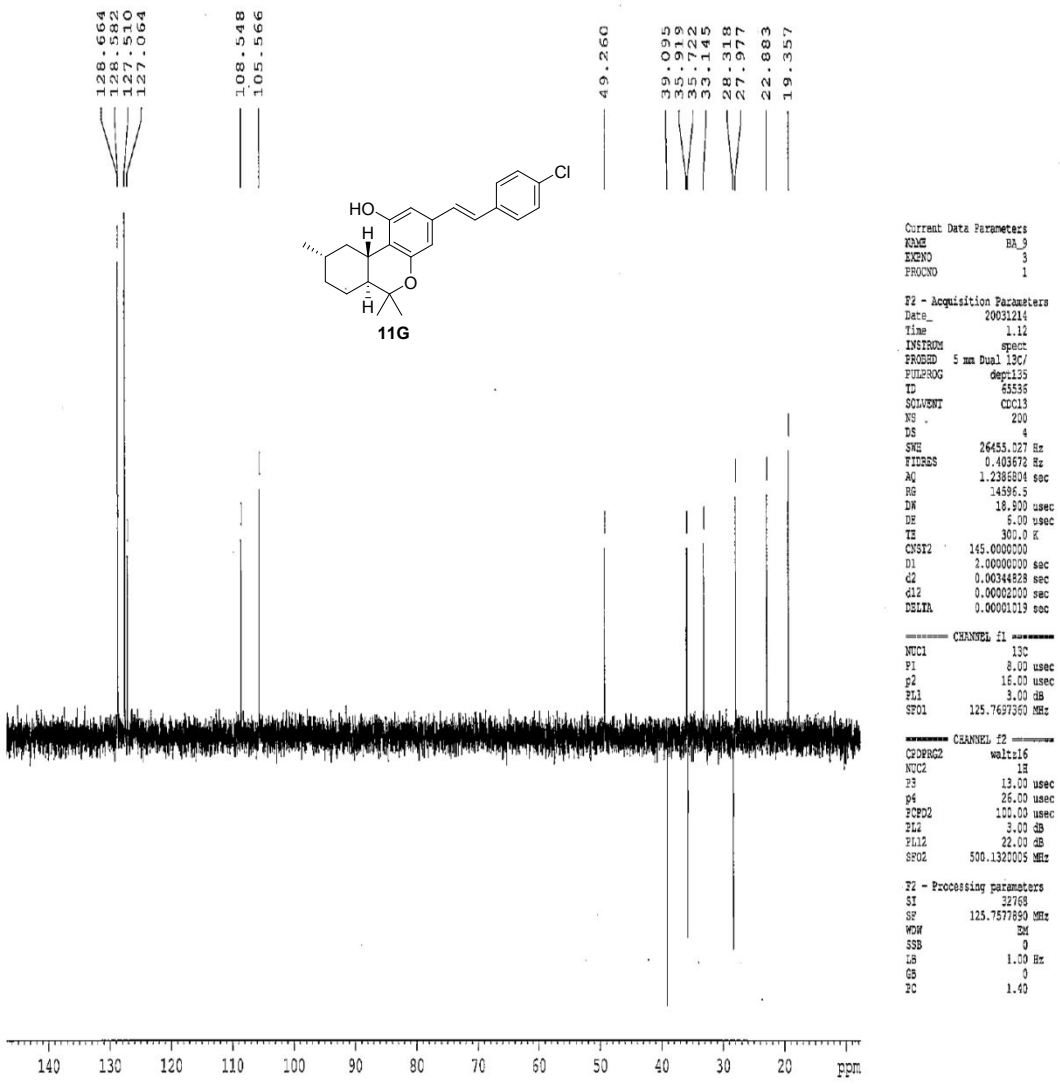


Figure S11d. HR-MS of compound **11G**

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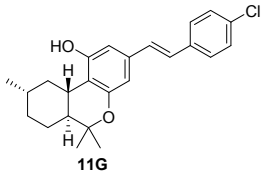
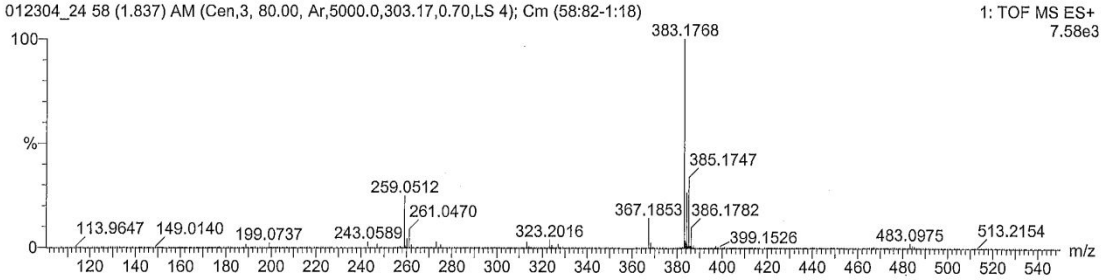


11G

Single Mass Analysis (displaying only valid results)
Tolerance = 30.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

ba-9
012304_24 58 (1.837) AM (Cen,3, 80.00, Ar,5000.0,303.17,0.70,LS 4); Cm (58:82-1:18) 1: TOF MS ES+ 7.58e3



Minimum:				-1.5		
Maximum:		200.0	30.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
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Figure S12a. [1]H NMR spectra of compound **11H**

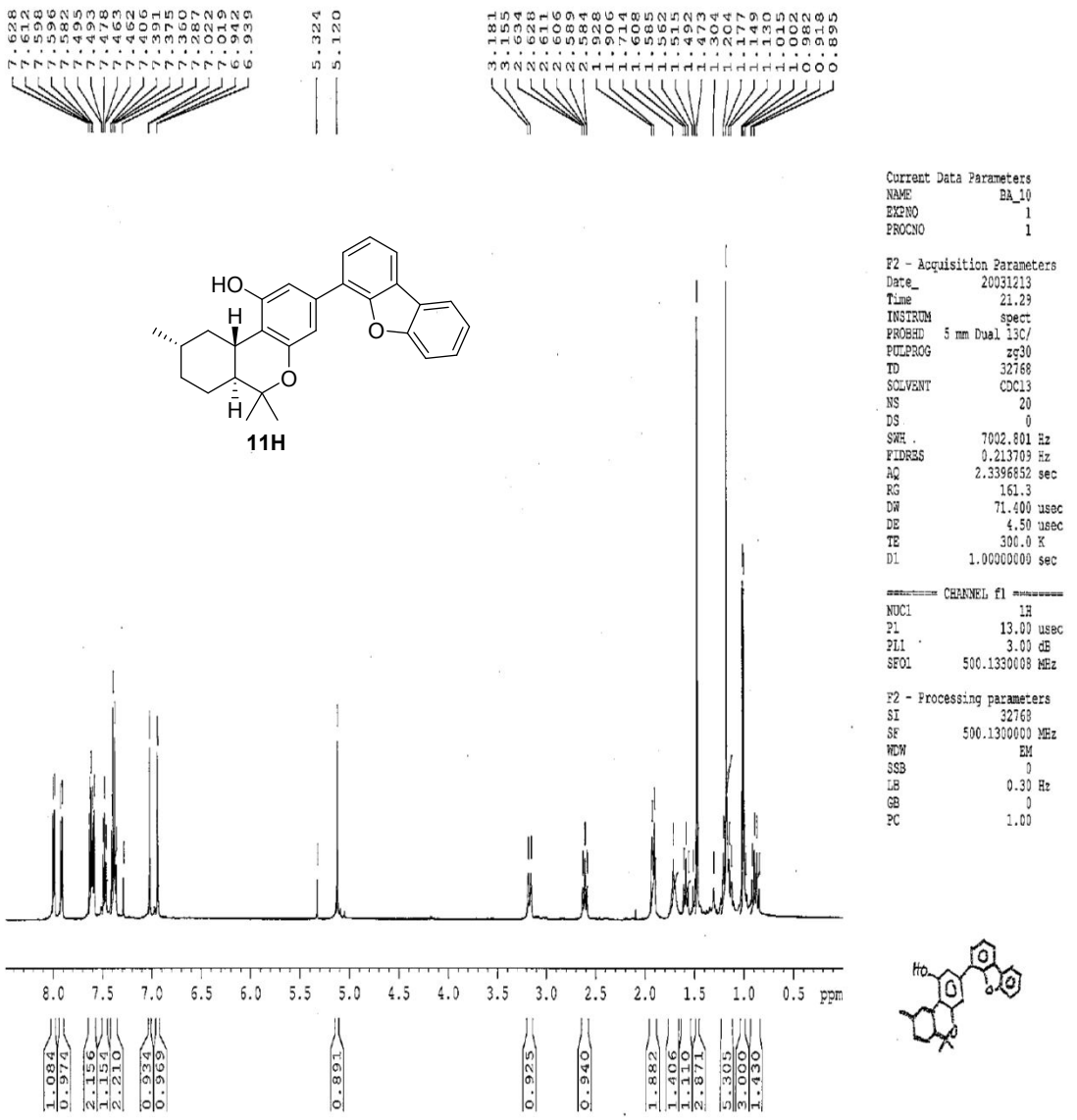


Figure S12b. ^{13}C NMR spectra of compound **11H**

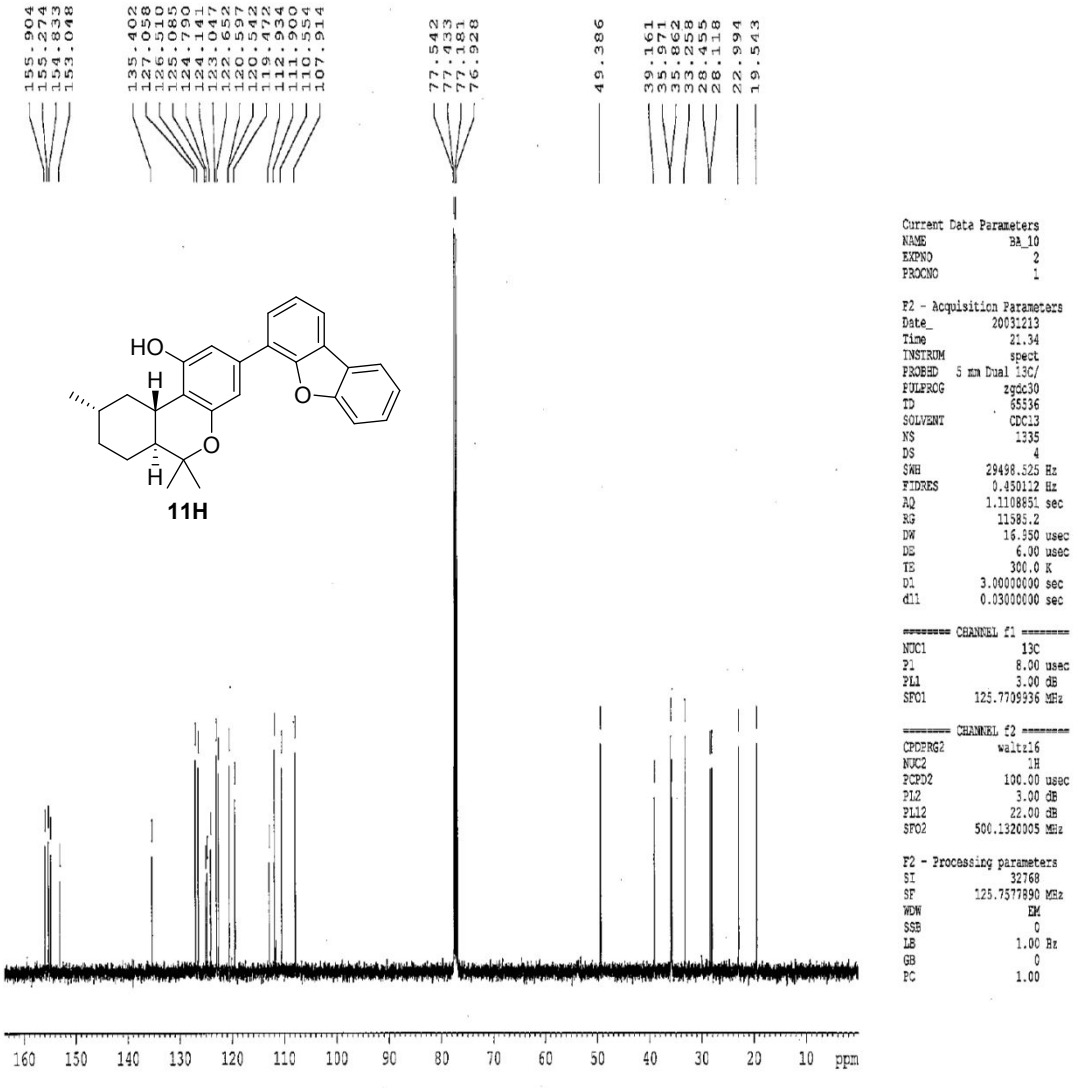


Figure S12c. DEPT-135 NMR spectra of compound **11H**

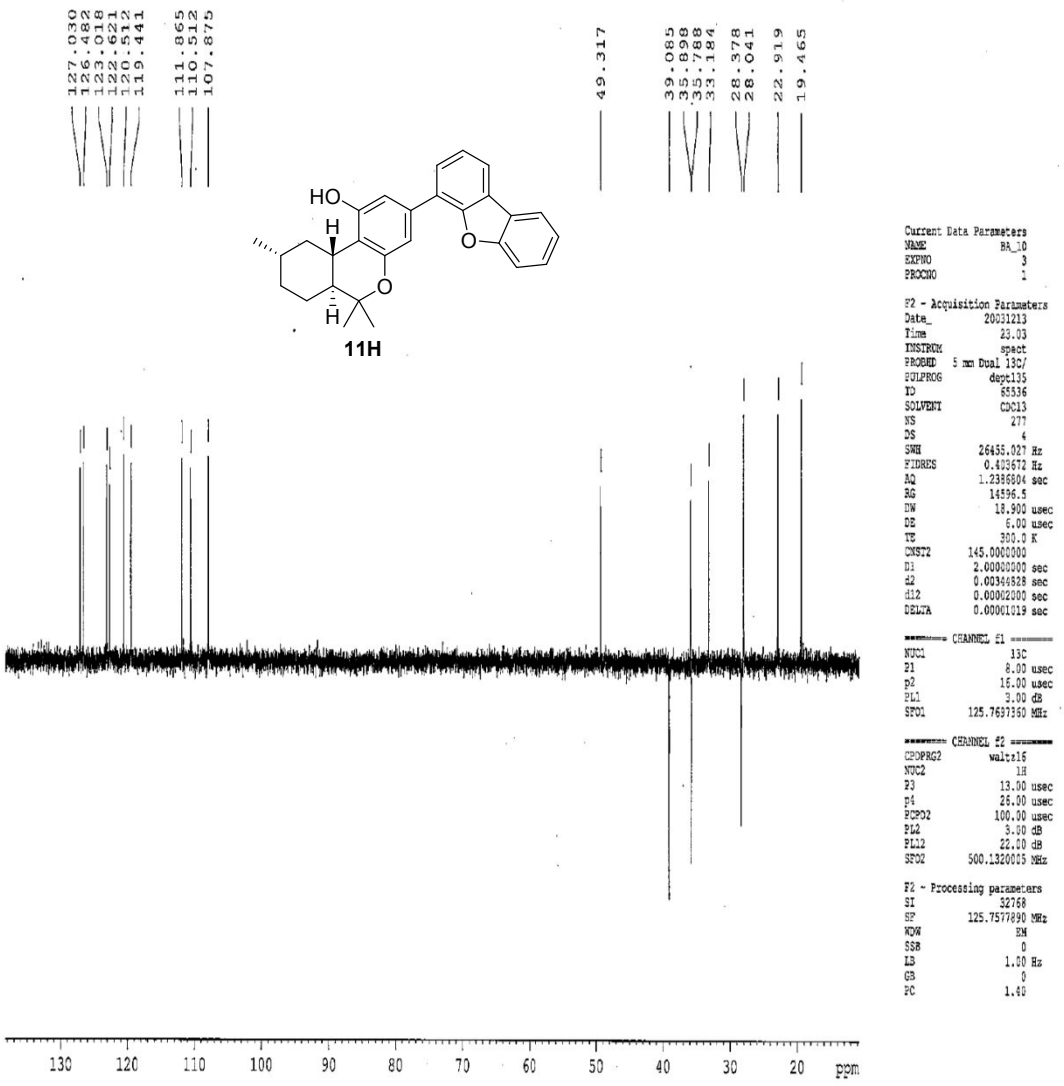
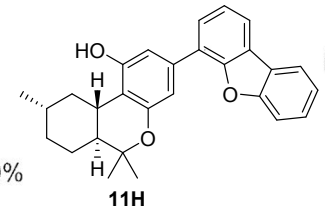


Figure S12d. HR-MS of compound **11H**



11H

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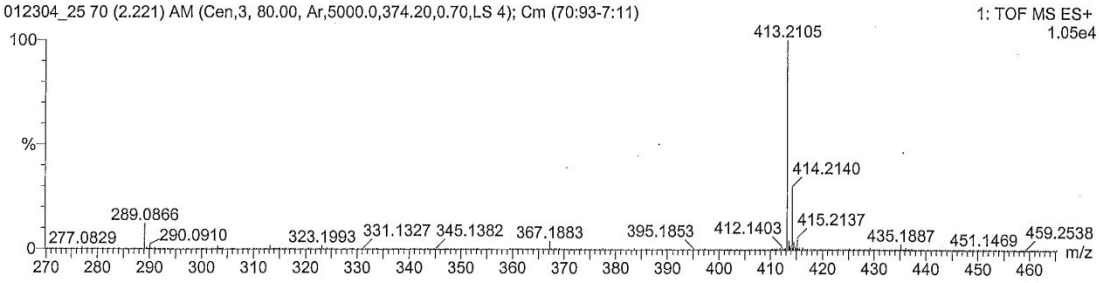
Single Mass Analysis (displaying only valid results)
Tolerance = 30.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

ba-10
012304_25 70 (2.221) AM (Cen,3, 80.00, Ar,5000.0,374.20,0.70,LS 4); Cm (70:93-7:11) 1: TOF MS ES+ 1.05e4



Minimum:				-1.5		
Maximum:		200.0	30.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
413.2105	413.2117	-1.2	-2.8	14.5	1	C28 H29 O3

Figure S13a. ^{1}H NMR spectra of compound **11I**

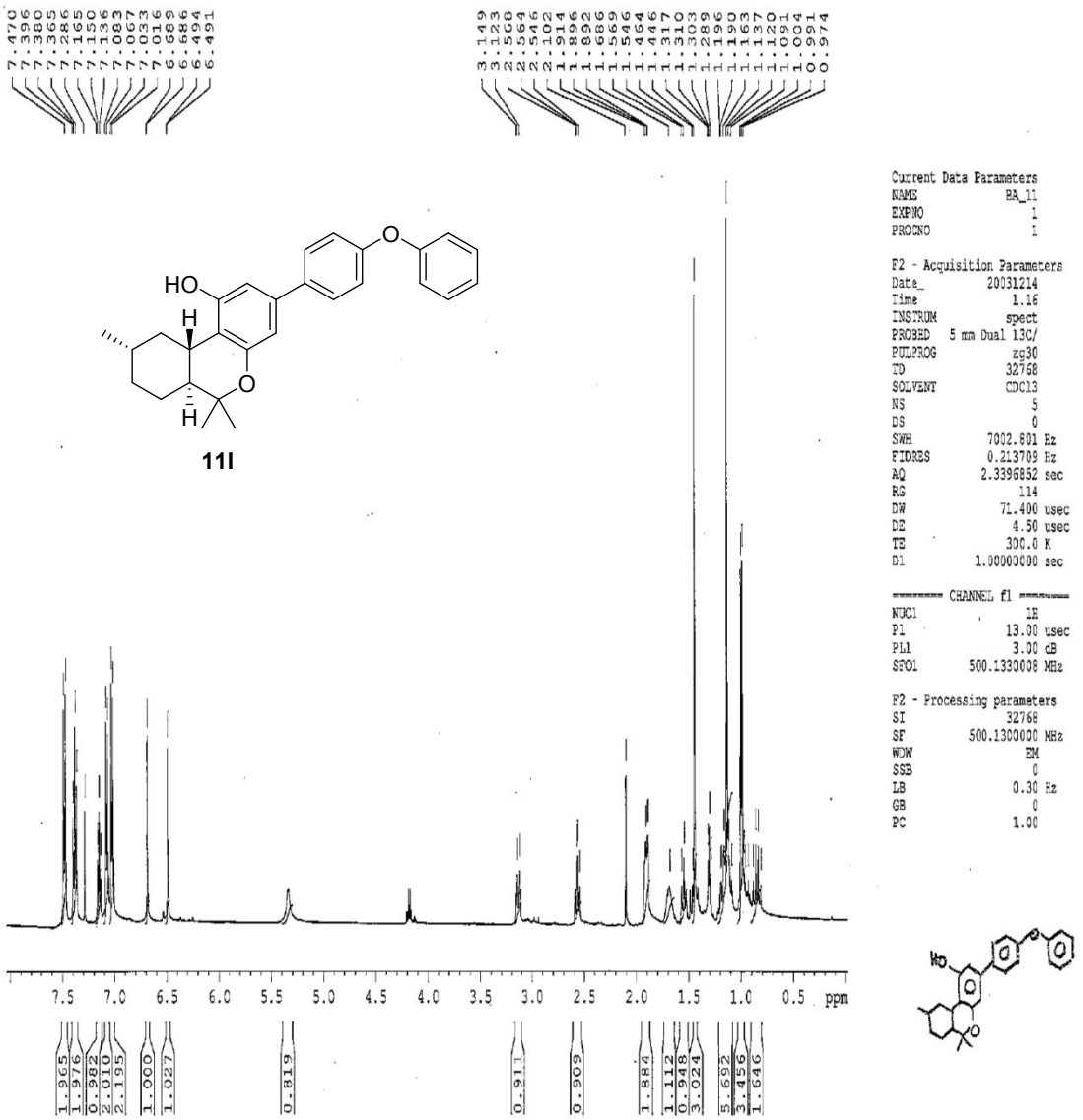


Figure S13b. ^{13}C NMR spectra of compound **11I**

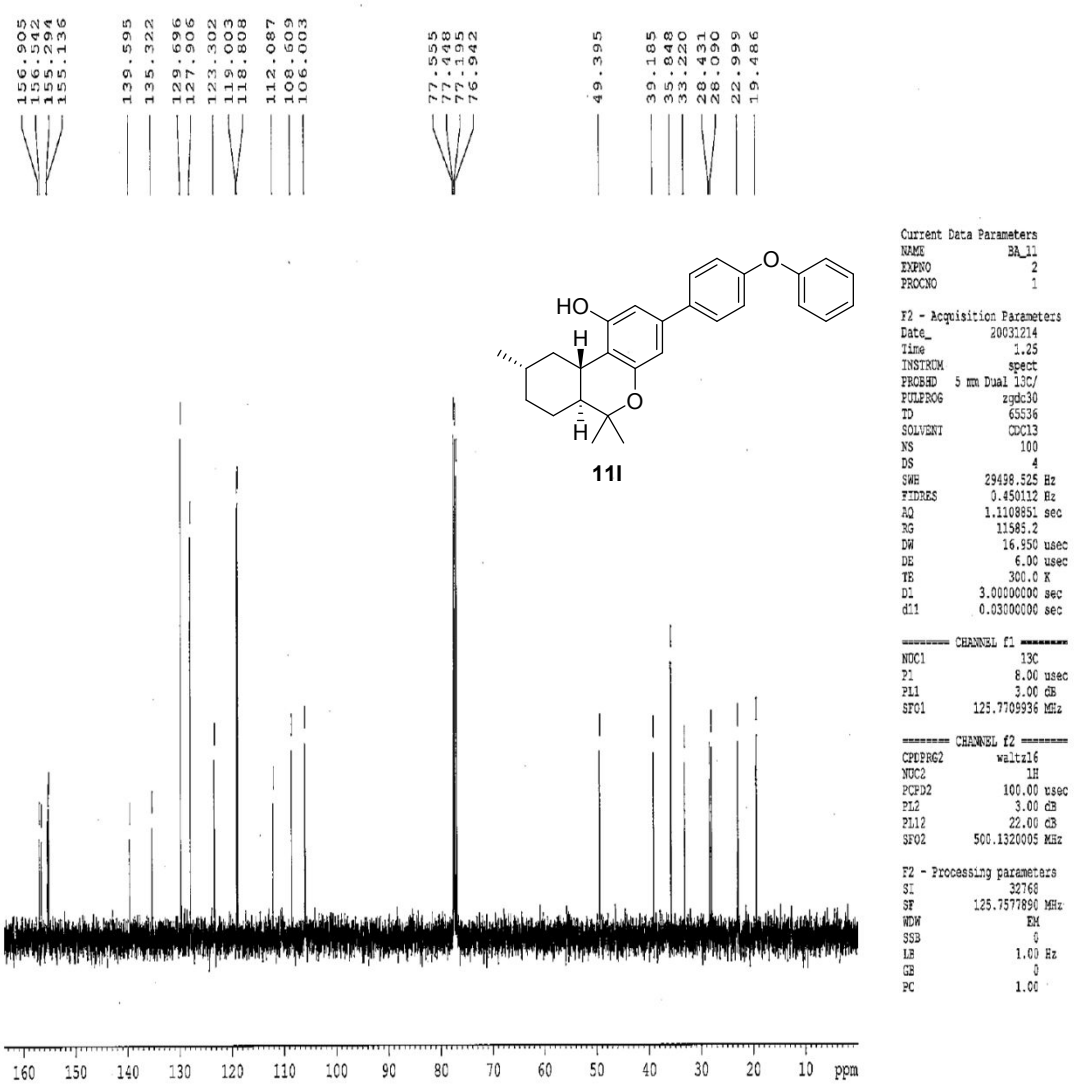
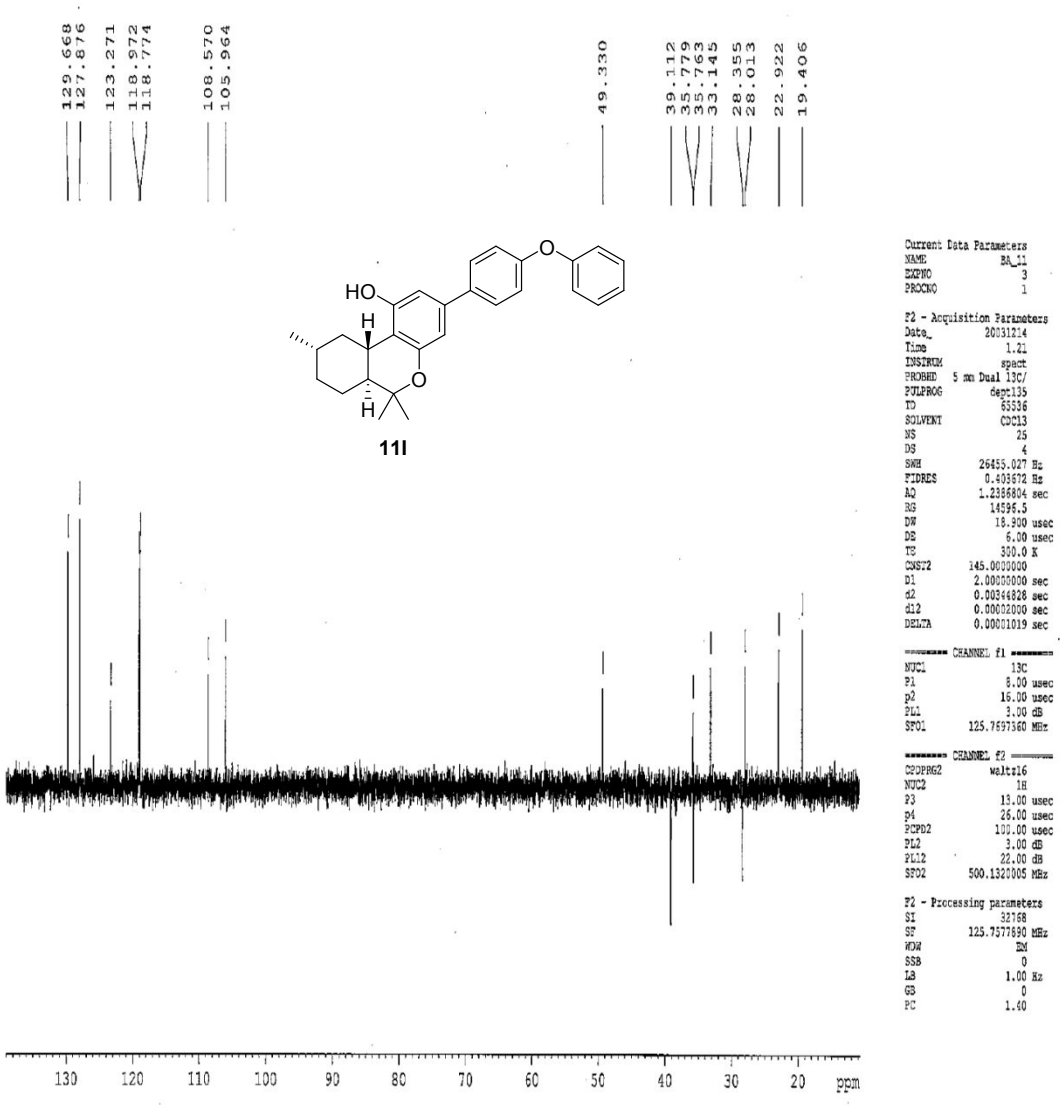


Figure S13c. DEPT-135 NMR spectra of compound **11I**



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PROCNO 1

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SOLVENT CDCl3
NS 25
DS 4
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FIDRES 0.403672 Hz
AQ 1.2386804 sec
RG 14596.5
DW 18.900 usec
DE 6.00 usec
TE 300.0 K
CNST2 145.0000000
D1 2.00000000 sec
d2 0.00344828 sec
d12 0.00002000 sec
DELTA 0.00001019 sec

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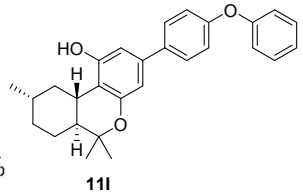
NUC1 13C
P1 8.00 usec
p2 16.00 usec
PL1 3.00 dB
SFO1 125.7697360 MHz

CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
P3 13.00 usec
p4 26.00 usec
PCPD2 100.00 usec
PL2 3.00 dB
PL12 22.00 dB
SFO2 500.1320005 MHz

F2 - Processing parameters
SI 32768
SF 125.7577690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Figure S13d. HR-MS of compound **11I**



11I

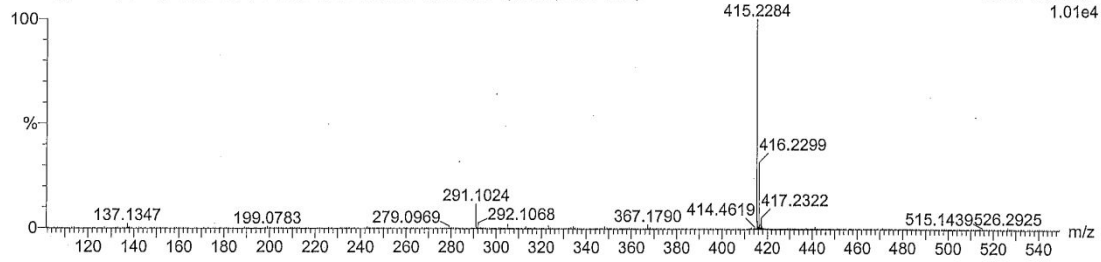
Elemental Composition Report Page 1

Single Mass Analysis (displaying only valid results)
Tolerance = 30.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

ba-11
012304_26 73 (2.310) AM (Cen,3, 80.00, Ar,5000.0,374.20,0.70,LS 4); Cm (73:93-9:13)

1: TOF MS ES+
1.01e4



Minimum:				-1.5		
Maximum:		200.0	30.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
415.2284	415.2273	1.0	2.5	13.5	1	C28 H31 O3

Figure S14a. ^{1}H NMR spectra of compound **11J**

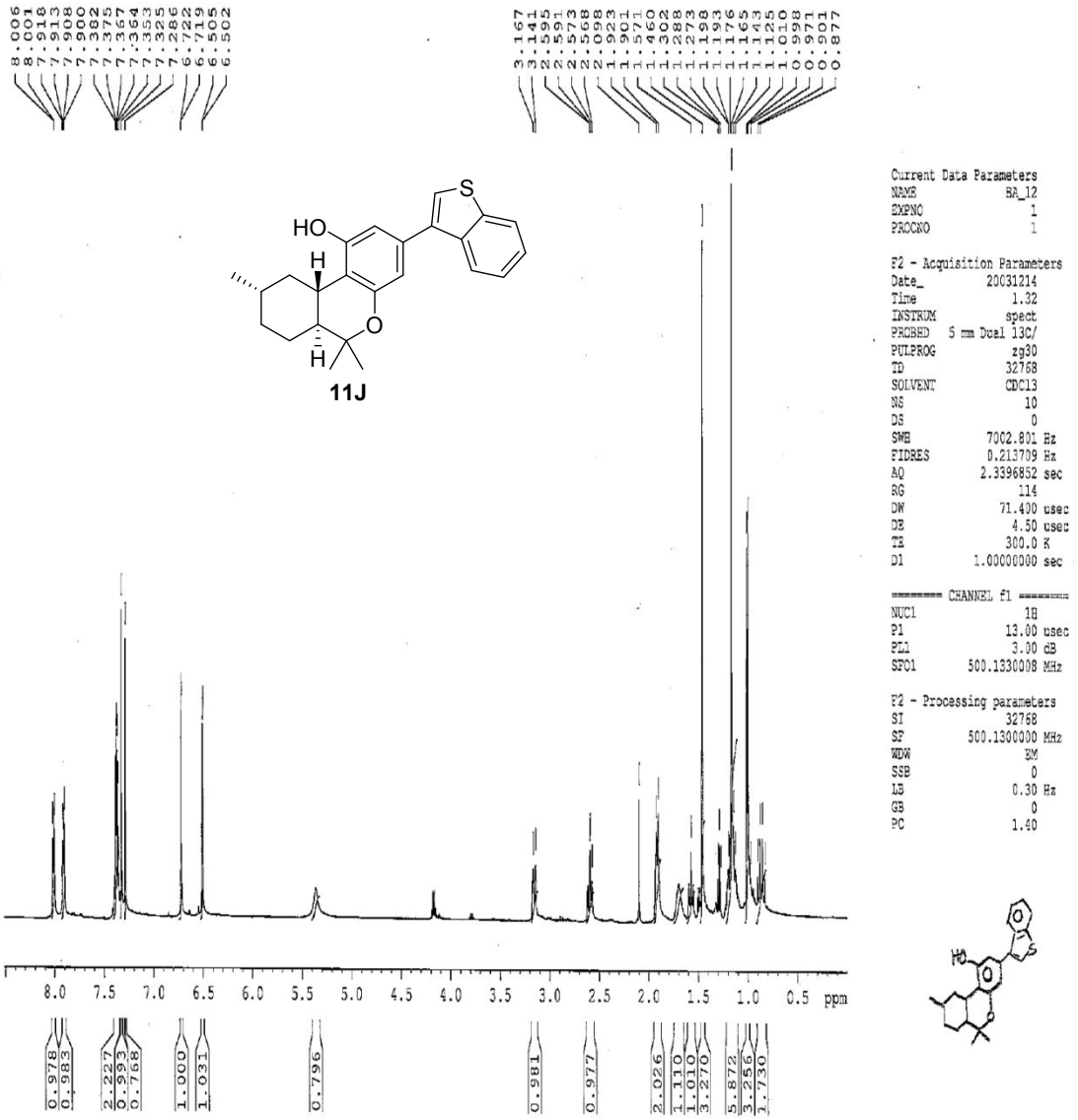


Figure S14b. ^{13}C NMR spectra of compound **11J**

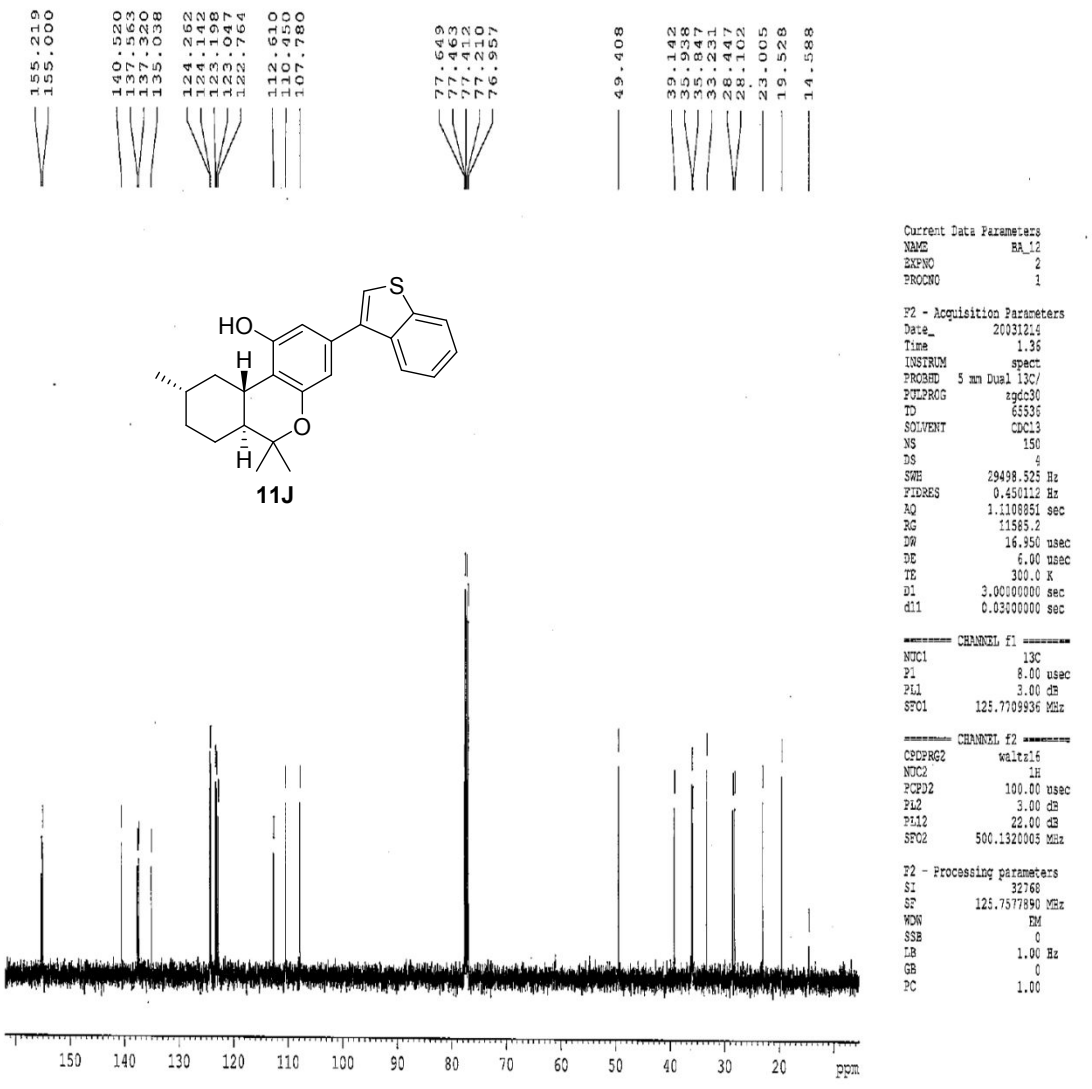
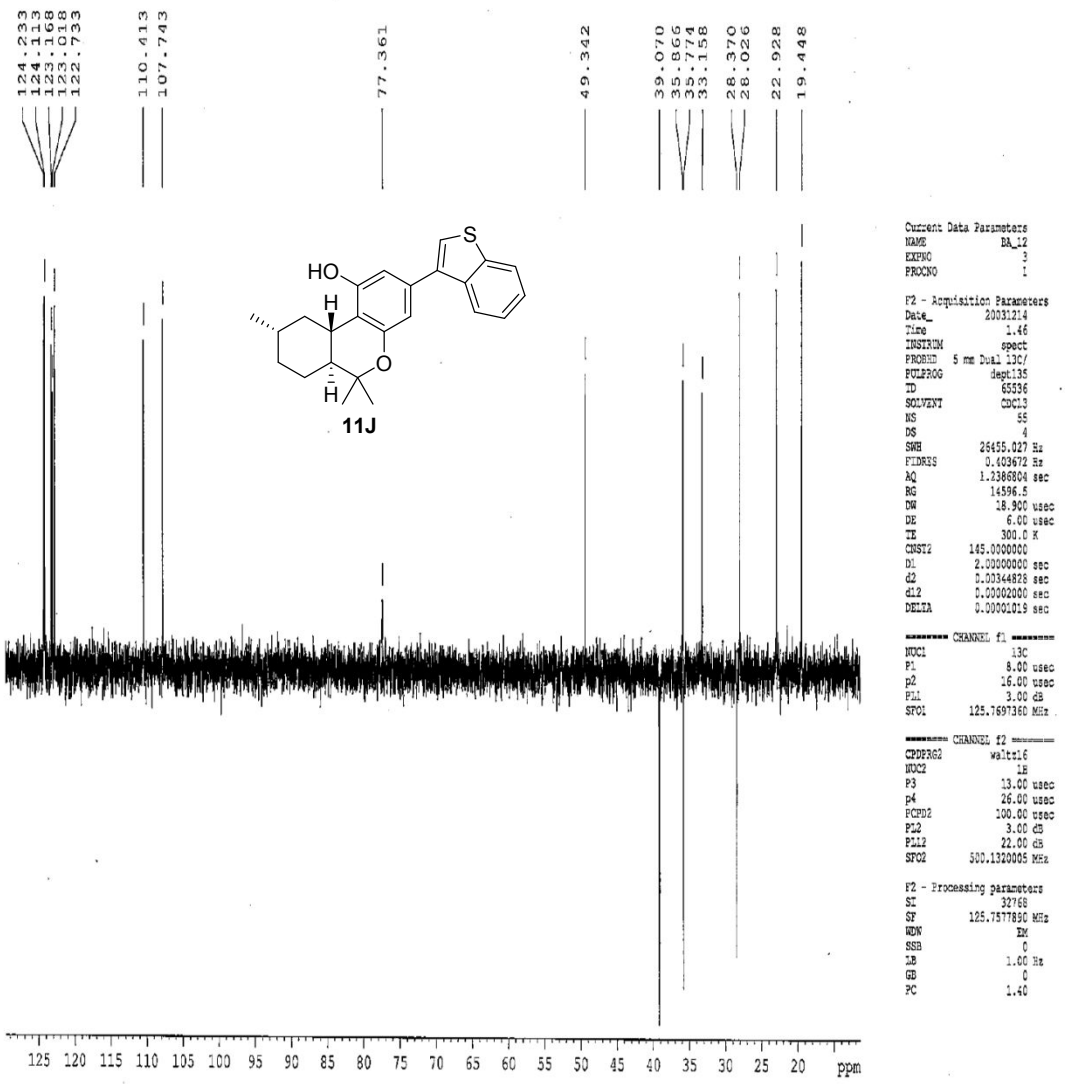


Figure S14c. DEPT-135 NMR spectra of compound **11J**

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PROCNO                    1

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TD                    65536
SOLVENT               CDCl3
NS                       55
DS                        4
SWH               28455.027 Hz
FIDRES             0.403672 Hz
AQ                 1.2386804 sec
RG                   14596.5
DW                  18.900 usec
DE                   6.00 usec
TE                   300.0 K
CNST2             145.0000000
D1                2.00000000 sec
d2                0.00344828 sec
d12               0.00002000 sec
DELTA             0.00001019 sec

====== CHANNEL f1 ======
NUC1                    13C
P1                    8.00 usec
p2                   16.00 usec
PL1                   3.00 dB
SFO1              125.7697360 MHz

====== CHANNEL f2 ======
CPDPRG2              waltz16
NUC2                    1H
P3                   13.00 usec
p4                   26.00 usec
PCPD2                100.00 usec
PL2                   3.00 dB
PL12                 22.00 dB
SFO2              500.1320005 MHz

F2 - Processing parameters
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SF                125.7577890 MHz
WDW                         EM
SSB                          0
LB                    1.00 Hz
GB                           0
PC                    1.40
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Figure S14d. HR-MS of compound **11J**

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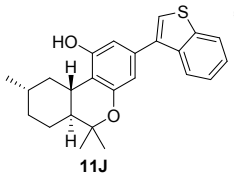
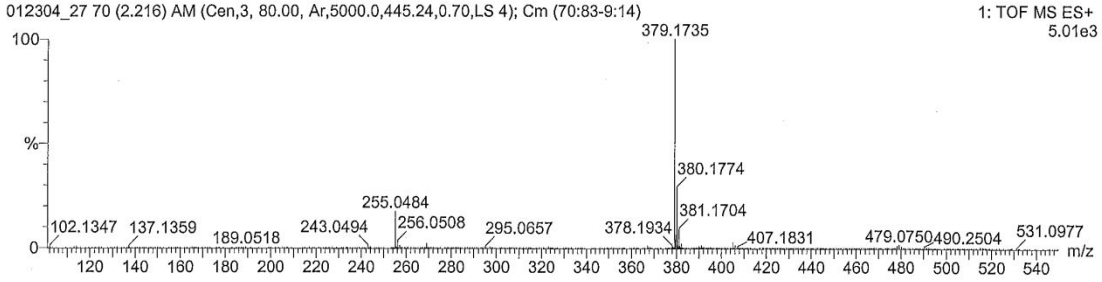


11J

Single Mass Analysis (displaying only valid results)
Tolerance = 30.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

ba-12
012304_27 70 (2.216) AM (Cen,3, 80.00, Ar,5000.0,445.24,0.70,LS 4); Cm (70:83-9:14) 1: TOF MS ES+ 5.01e3



Minimum:				-1.5		
Maximum:		200.0	30.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
379.1735	379.1732	0.3	0.9	11.5	1	C24 H27 O2 S

Figure S15a. [1]H NMR spectra of compound **11K**

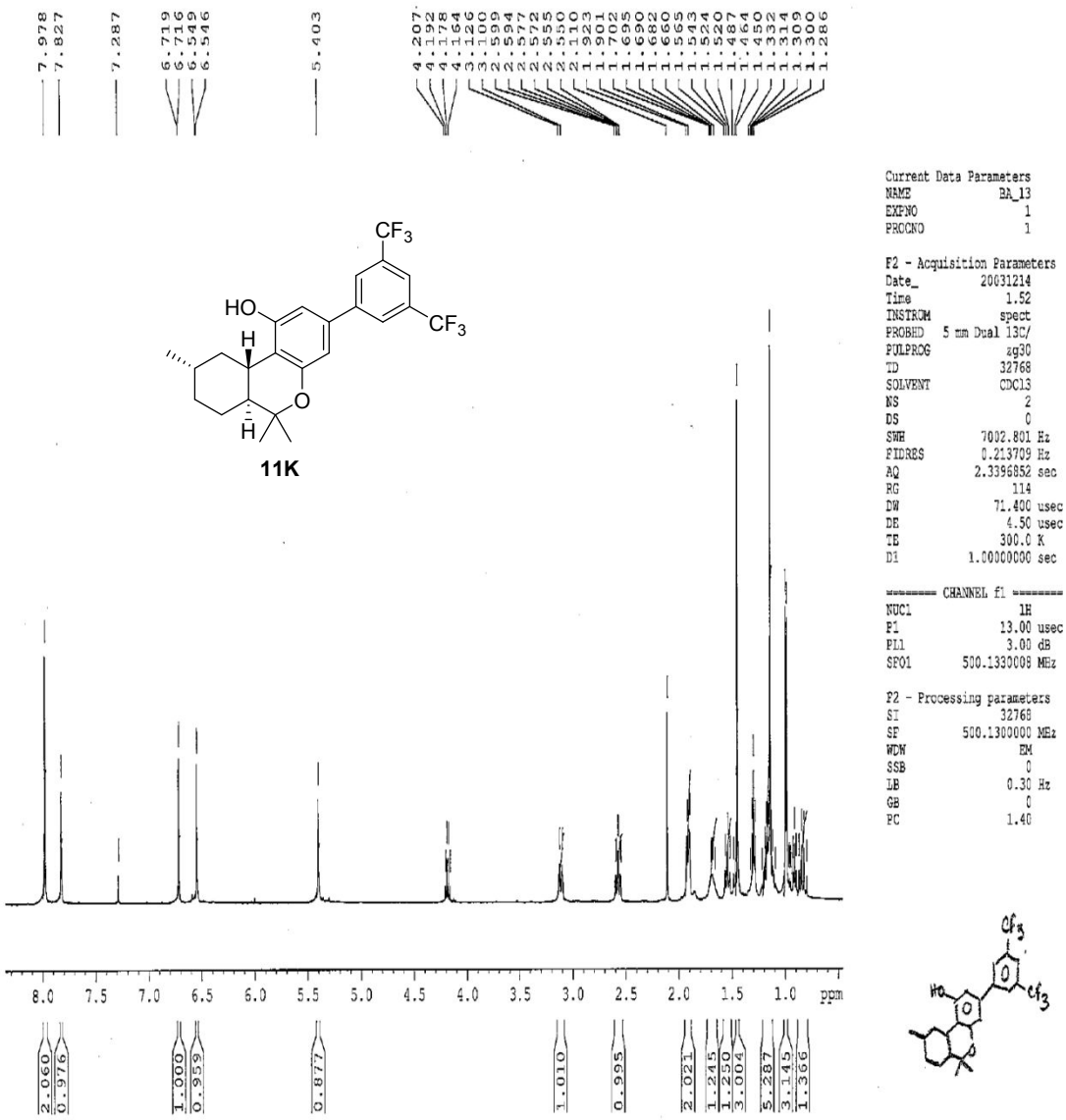


Figure S15b. ^{13}C NMR spectra of compound **11K**

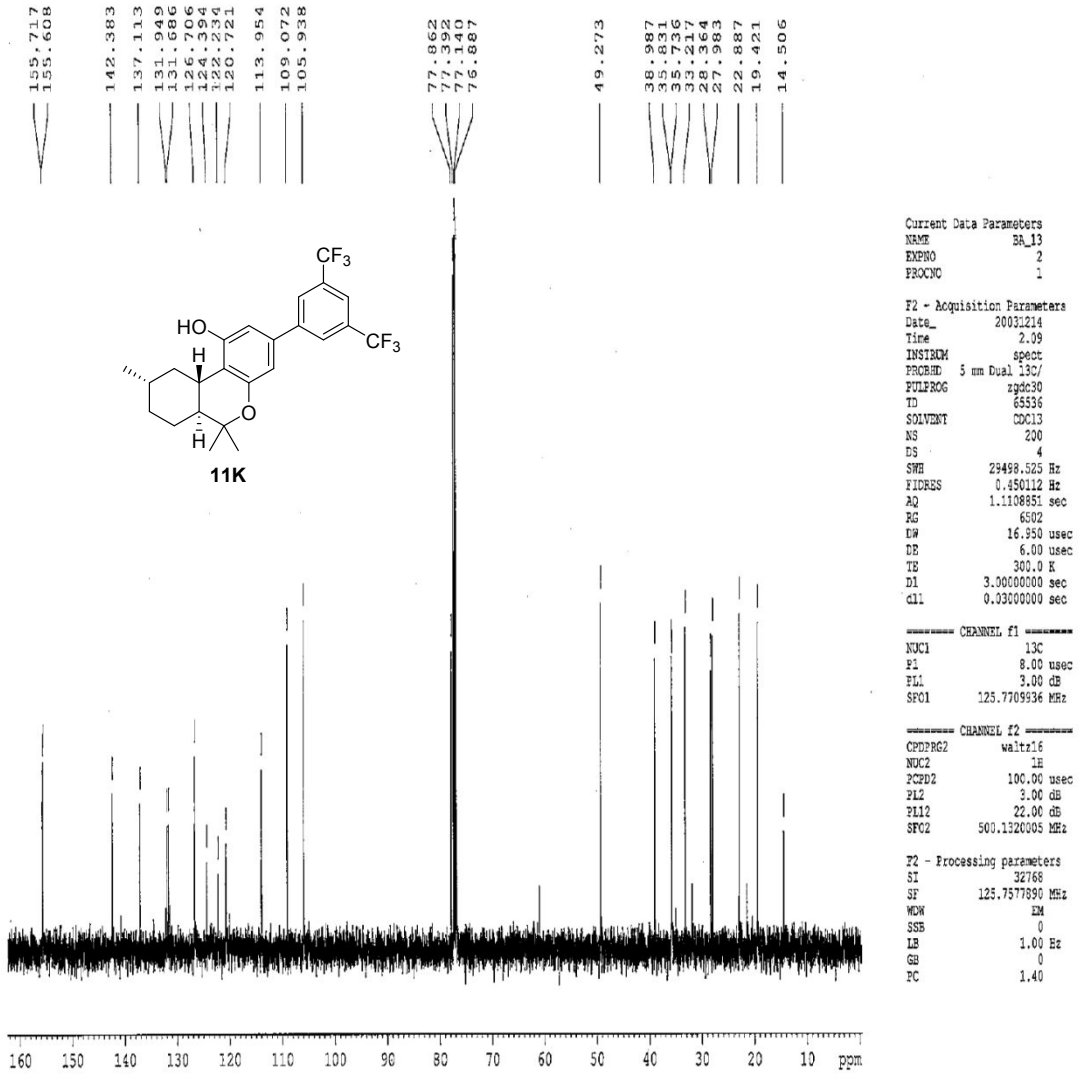


Figure S15c. DEPT-135 NMR spectra of compound **11K**

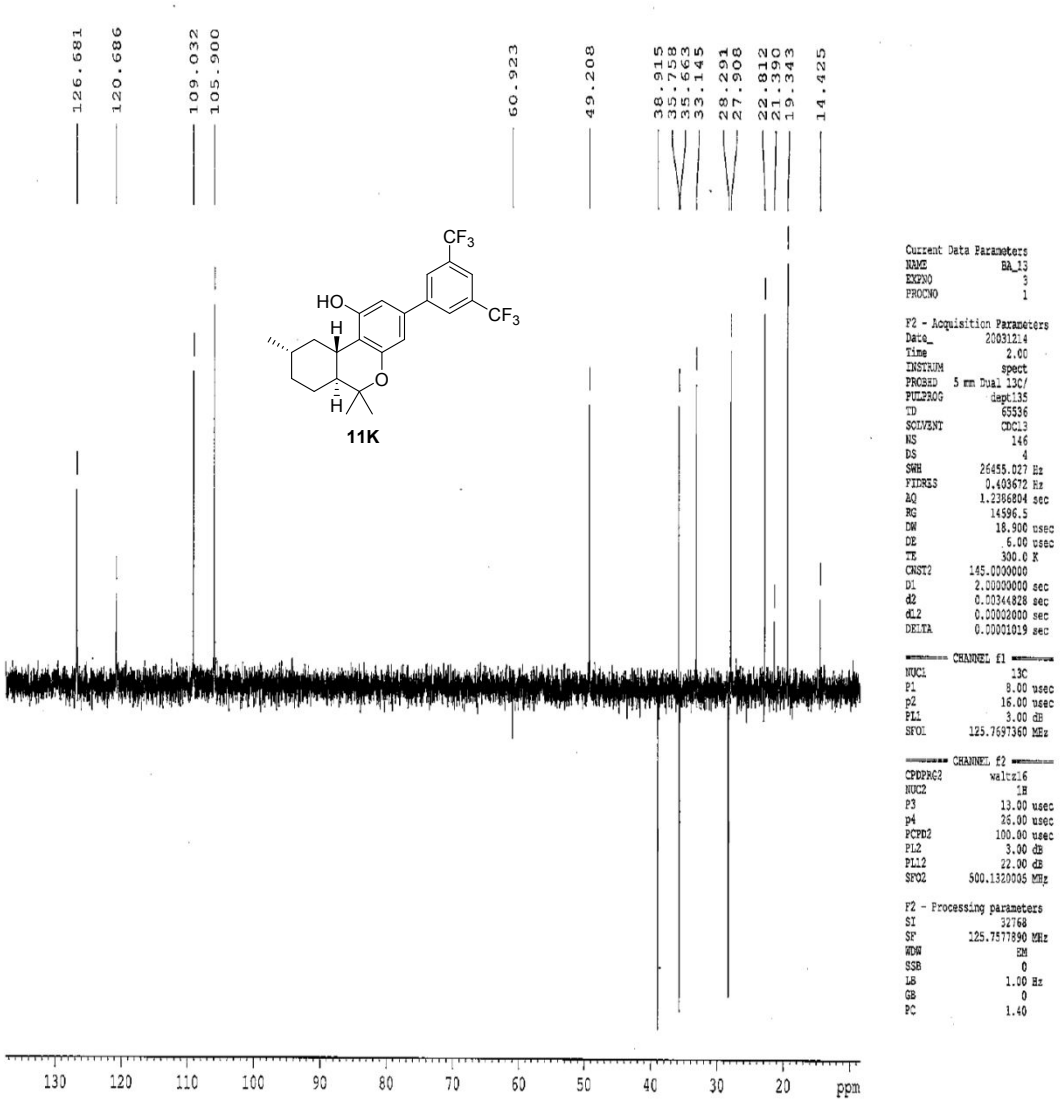
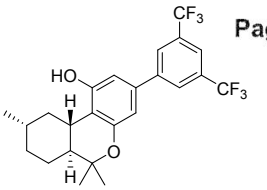


Figure S15d. HR-MS of compound **11K**

Elemental Composition Report Page 1

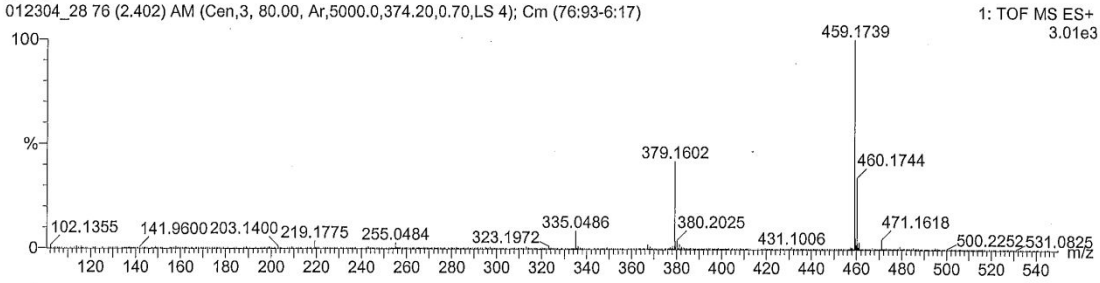
Single Mass Analysis (displaying only valid results)
Tolerance = 30.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Even Electron Ions
6 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)



11K

ba-13
012304_28 76 (2.402) AM (Cen,3, 80.00, Ar,5000.0,374.20,0.70,LS 4); Cm (76:93-6:17)



Minimum:				-1.5		
Maximum:		200.0	30.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
459.1739	459.1759	-2.0	-4.3	9.5	1	C24 H25 O2 F6